

Görel Östberg

ON ARTERITIS
WITH SPECIAL REFERENCE
TO POLYMYALGIA
ARTERITICA

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WITH SPECIAL REFERENCE TO
POLYMYALGIA ARTERITICA**

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FROM THE UNIVERSITY DEPARTMENT OF PATHOLOGY, GENERAL HOSPITAL,
MALMÖ, SWEDEN

On arteritis
with special reference
to polymyalgia arteritica

BY

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Translated by Mr. L. James Brown



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This thesis concerns the morphological changes in the large arteries in patients with the clinical picture of polymyalgia arteritica. Some other arterial diseases of differential diagnostic interest are also described and discussed. Frequency analyses of arteritis in necropsy cases were performed and are discussed. Literature on different arteritis entities is reviewed. The work is partly based on two former publications:

- I Östberg, G.: Morphological changes in the large arteries in polymyalgia arteritica. *Acta med. scand. Suppl.* 533, 135—164, 1972.
- II Östberg, G.: Temporal arteritis in a large necropsy series. *Ann. rheum. dis.* 30, 224—235, 1971.

CHAPTER I

INTRODUCTION

By far the most common arterial changes seen by a clinical pathologist are those of arteriosclerosis, which are probably degenerative in nature and of complex aetiology. Despite intense and extensive investigation, their causation still challenges research. In several cases, however, they might be secondary to some (unknown) primary disease. In his thesis on aortic aneurysms, published in Stockholm in 1888, Karl Malmsten reported that it had been known for some years (Walshe 1873) that syphilis could cause aortic changes. Syphilitic aortitis has since been observed with varying frequency, which has, however, declined since the advent of chemotherapy and antibiotics. Syphilitic aortitis has been thought to explain "inverse arteriosclerosis" with more pronounced atheromatous and calcified changes in the proximal part of the aorta than in the distal part, where such changes are otherwise more marked. Since the 1930s a further type of arteritis and aortitis has been known (Barnard, 1935). This type was called giant-cell aortitis because of the characteristic microscopic changes, which were apparently first observed by Horton et al. (1934), Horton and Magath (1937) in temporal arteries. — Arteritis and aortitis are fairly rare, compared with arteriosclerosis, but little is known of their frequency because the cases on record were discovered more or less incidentally, and

no systematic attempt has been made to estimate their incidence. — My interest in arteritis was aroused mainly by the opportunity I had to study arterial changes in a clinically well examined material published by Hamrin (1972) (I). I had already before that time utilised the good possibilities available at the Institute of Pathology, Malmö, for frequency studies and had analysed a 1-year necropsy series of temporal arteritis and published the results in 1971 (II). These investigations have since been supplemented by further studies of arterial changes and their frequency.

This investigation concerns:

1. the arterial changes, their type and extent in patients with polymyalgia arteritica,
2. changes in other types of arteritis from a differential-diagnostic point of view,
3. the significance of arteritis in the clinical picture,
4. the frequency of arteritis and some other arterial changes in a routine necropsy series (retrospective study).
5. the frequency of arteritis of the aorta and of the aorta + temporal arteries, respectively, in consecutive series (prospective studies), and
6. formerly described types of arteritis, and their characteristics. — Is polymyalgia arteritica an independent and new variant of arteritis?

CHAPTER II

MORPHOLOGICAL CHANGES IN THE LARGE ARTERIES IN POLYMYALGIA ARTERITICA (PAPER I)

INTRODUCTION

Between 1952 and 1968 Bengt Hamrin, a physician, collected cases of temporal arteritis and polymyalgia rheumatica in Malmö and in Växjö (Hamrin, 1972). He found that a high percentage of patients with polymyalgia had signs of widespread arteritis and introduced the name of polymyalgia arteritica, which is more adequate (Hamrin et al., 1964). It was evident that the greater the interest of clinicians in this disease and its clinical picture the more often it was diagnosed. For instance, during a 7½ year period as many as 94 cases of the condition were diagnosed in Växjö, in a population of about 100,000 persons which gave an incidence of 12 cases /100,000 persons/ year. The dominating clinical symptoms were pain, especially in the shoulder — but also in the pelvic girdle, fever and general malaise. The E. S. R. was also invariably raised, about 100 mm/l hr. The course of the disease was carefully followed and was found to last for several years. Most of the patients were treated with adrenocortical steroids, which usually produced a dramatic improvement. But treatment had to be continued for a very long time. — It was in association with those clinical studies that I had the opportunity to study the morphological changes in the patients who had died.

MATERIAL AND METHODS

In 16 cases the arterial system was examined systematically in transverse sections from the aortic root to the base of the skull, the areas of the elbow and of the knee, respectively (17-175 sections, average 100 sections per case). Eight of the patients had been followed up clinically by Hamrin, four had had temporal arteritis some years before death and in two cases necropsy revealed gross aortic changes, provisionally interpreted as arteritis, which was confirmed at microscopic examination. Two patients with polyarteritis nodosa, diagnosed 2 and 3 months, respectively, before death, had no gross changes in the large arteries. They were, however, examined in the same way as the others.

RESULTS

Macroscopic examination revealed in more than half of the cases a remarkable, diffuse intimal thickening and wrinkling of the aorta, which was most pronounced proximally. In four cases the aorta, especially the ascending part, was dilated. One patient had a longitu-

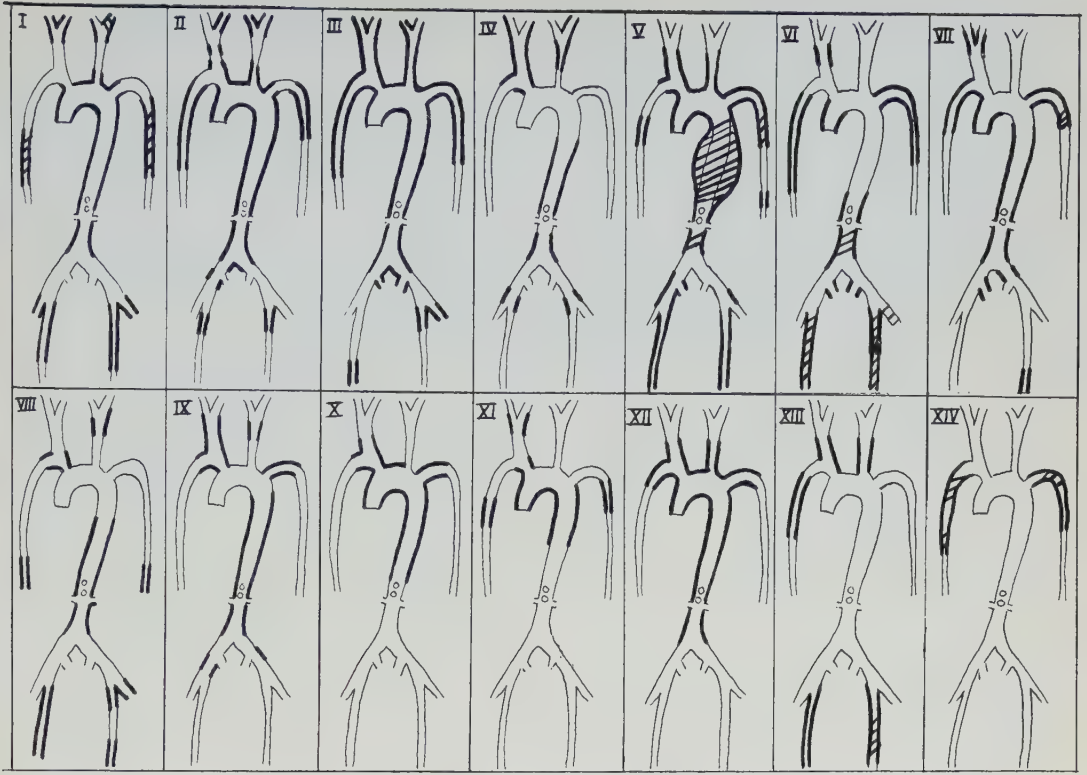


Fig. II:1.
Diagrams of findings in cases I—XIV, paper I. Arteritis marked by thick contours, thrombosis by hatching.

dinal aneurysm in the descending thoracic aorta and died from rupture of the thin wall of the aneurysm. — In four cases there was a narrowing of the arm arteries, in the proximal and distal part of the axilla; in two, a narrowing of the left subclavian artery immediately after its origin.

The most striking microscopical change, which was observed to a varying extent in all cases was medial necroses. Haematoxylin-eosin-stained sections showed areas of increased eosinophilia with loss of nuclei: sections stained for elastin, a thickening and collapse of the lamellae. A varying degree of inflammatory reaction with infiltrates of

lymphocytes and plasma cells was seen. The necrotic parts often showed breaks with massive deposition of lymphocytes and plasma cells and, in some cases, multinucleated giant cells around ends of broken lamellae.

Changes in the intima consisted of a generalised or local thickening with inwardly bulging cushion-like foci of loose connective tissue with relatively small nuclei.

The adventitia showed mild fibrosis of a varying degree, sometimes small clusters of round cells. No changes in the vasa vasorum were ever seen.

The extent of the changes was recorded and is given schematically in Fig. II:1. They

were most common in the aorta, they were sometimes found continuously in sections from the ascending aorta and down into descending and abdominal aorta; in other cases, with alternating, apparently unchanged areas between affected regions. In most cases changes were found in the arm arteries, somewhat less often in the iliac and leg arteries. The lesions were focal and were found only in parts of a transverse section, the areas affected varying from one section to the other. Serial sectioning was not performed.

The patients were 65 to 88 years old. One young female, aged 17 years, had a condition which was clinically diagnosed as Morbus Takayasu and which showed essentially similar changes in the large arteries. — Four patients died of what may be regarded as complications of aortitis, in most of the cases, however, aortitis had not notably contributed to death. — Two women, aged 56 and 57 years, in whom polyarteritis nodosa had been diagnosed, showed no changes in the large arteries.

CONCLUDING REMARKS

Polymyalgia arteritica with or without temporal arteritis appears to be a generalised arteritis with changes mainly in aorta, but also in its larger branches, more often localised in the brachiocephal parts than in the caudal. The lesions in the arteries are patchy and seem not to spread by extension. They are often found only in some parts of a transverse section of the artery. — The lesions appear primarily in the medial coat, most often in its outer parts. In early cases oedema with round cell infiltration is seen; later on, patchy necroses with disappeared nuclei and coarse elastic lamellae. Inflammatory cells, mainly lymphocytes and plasma cells, accumulate around breaks in these necrotic parts of media. Multinucleated giant cells may be found but appear not to be an essential factor. — Polymyalgia arteritica is a chronic disease, which does not seem to shorten the expectation of life. Some cases were complicated by aortic rupture.

CHAPTER III

FURTHER SYSTEMATIC INVESTIGATIONS OF CASES OF ARTERITIS

INTRODUCTION

In the further analysis of the arteritis material it was considered of interest to elucidate the morphological changes in the large arteries with those in some additional cases of arteritis of different origin to obtain a firmer basis for differentiation.

MATERIAL

This series consisted of 16 cases, most of which were collected in the years 1971 and 1972. One case of dissecting aortic aneurysm with medial necrosis in association with Marfan's syndrome, seen in 1961, was also included. Five patients had previously known temporal arteritis which, in four of them, had been confirmed by biopsy. Two patients had no previously known arteritis, but gross aortic changes at necropsy suggested arteritis. One patient had an old rheumatic affection with valvular disease, one juvenile rheumatoid arthritis and one spondylarthritis. Five cases of clinically known and serologically verified syphilis were

included, and one case of aortic rupture in Marfan's syndrome. The age- and sex distribution, the clinical diagnosis, treatment and main causes of death are given in tabular form (Table III:1).

METHODS

The large arteries were treated in the same way as in the previous investigation (1). Transverse sections of the vessels were examined, and in most cases longitudinal sections were cut towards the aortic valves. The carotid arteries were removed to the base of the skull; the arm arteries, to the distal axilla (thus not to the area of the elbow, as was usually the case in the previous investigation). The femoral arteries were examined to the distal third of the thigh. The sections were stained with haematoxylin-eosin and, if the findings proved interesting, also for elastin. In some cases toluidine-blue was used for demonstration of metachromasia. Nineteen (case 16) to 184 (case 8) transverse sections were studied per case, on the average 105 sections per case.

Table III:1

Case nr	Sex	Age (death)	Clin diagnosis	Temp. biopsy	Interval (years)	Steroid treatment	Main cause of death
1	F	77	Incomp. cordis	+ 1971	8/12	6 mths 1971-72	Myocardial necroses, Incomp. cordis.
2	F	85	Temp. arteritis Incomp. cordis Gangraena cruris		2/12	2 mths 1972-death	Incomp. cordis, Arteritis, Gangraena cruris.
3	M	82	Infarctus myocardii?				Morbus arteriosclerot. cordis, Aneurysma aortae.
4	F	86	Laesio vascularis cerebri? Oedema pulmonis	+ 1961	13	1959-1969	Astrocytoma cerebri.
5	F	72	Stenosis valv. mitralis	Temp. art. 1963?	9 ?		Aortitis, Ruptura aortae.
6	F	78	Uræmia, Pyelonephritis	+ 1967	4	1967-death-71	Infarctus myocardii.
7	F	84	Incomp. cordis	+ 1970	9/12	9 mths 1970-death	Coronary sclerosis, Infarctus myocardii.
8	M	53	Stenosis et insuff. valv. aortae				Insuff. valv. aortae, Aortitis.
9	F	22	Arthritis rheum.				Haemorrhagia pulmonis, Arthritis rheumatoid.
10	M	56	Spondylarthrit. Infarctus myocardii				Infarctus myocardii.

Cases studied systematically with clinical data. Interval = time in years between onset of symptoms and death.

+ arteritis diagnosed in biopsy specimen.

— no arteritis

.... no investigation

TPI = treponema pallidum immobilisation test.

FTA = fluorescent treponemal antibodies.

CASE HISTORIES

Case nr	Sex	Age (death)	Clin. diagnosis	Syphil. infect.	WR	Treatment	Main cause of death
11	F	73	Aortic valv. disease (syphilitic)	?	+	Penicillin	Insuff. valv. aortae.
12	F	80	Aortic valv. disease (syphilitic)	?	+	—	Stenosis + insuff. valv. aortae.
13	F	74	Mors subita cerebri? cordis?	1919	+	Hg 1919, 1928?	Ruptura aortae. Aortitis.
14	M	80	Bronchitis chron.	?	+	—	Bronchitis chron.
15	M	68	Infarctus myocardii	1932	Kline + 1972 FTA, TPI + 1972	Local 1932 Fever 1958	Infarctus myocardii.
16	F	24	Marfan's syndrome				Ruptura aortae.

Case 1, a woman, born in 1895. — In the summer of 1971 she had diffuse joint symptoms and an unsteady gait. In the autumn headache supervened, particularly over the eyes and behind the ears. The pain gradually extended towards the region of the jaws and the temples. The E.S.R. rose to 73 mm/l hr. — Tender nodules appeared along the temporal arteries and histological examination of a biopsy specimen showed arteritis. No eye changes. — Responded promptly to prednisolone. — In the spring and summer of 1972 she had symptoms of cardiac insufficiency, and was admitted to hospital at the end of July. Despite treatment she deteriorated and died on the sixth day after admission.

E.S.R. in December 1971 was 90 mm/l hr, after which it fell to 16—40 mm/l hr. In April 1972 it was 55-68-10 mm/l hr. In June 1972 it was 25-40-23-14 mm/l hr. In July 1972 29-10 mm/l hr.

Necropsy: The aortic arch and the descending aorta showed mild arteriosclerosis with yellow-white plaques and mild diffuse wrinkling. There was a slight narrowing of the axillary part of the arm arteries. The heart was somewhat enlarged, the myocardium was pale, no infarcts and no scars.

Microscopical findings: Arteritis in the aorta. (Figs. III: 1, 2, 3, 4, 5). — Small fibrous scars and areas of necrosis in the myocardium. Chronic congestion in the lungs, liver and spleen.

Cause of death: Myocardial necroses, cardiac insufficiency.

Case 2, a woman, born in 1887. — Previously healthy. From April 1972 treated with steroids because of temporal arteritis (no biopsy). Admitted to hospital in June 1972 with signs of arterial thrombosis in the right lower leg. During 14 days' conservative treatment the patient deteriorated and died.

Necropsy: Aorta of normal width with smooth intima. Branches of the arch were of normal width and configuration. Moderate atheromatosis in distal aorta, moderate wrinkling and calcareous deposits proximally in both femoral arteries. In the region of the knee the right femoral artery was obstructed by a thrombus, 4—7 mm in diameter, partly adherent to the wall and undergoing disintegration. — Fibrous scars after infarcts in the lateral wall of left ventricle, signs of cardiac failure with pulmonary oedema and general congestion.

Microscopical findings: Sequelae after arteritis of aorta and its large branches, including the femoral

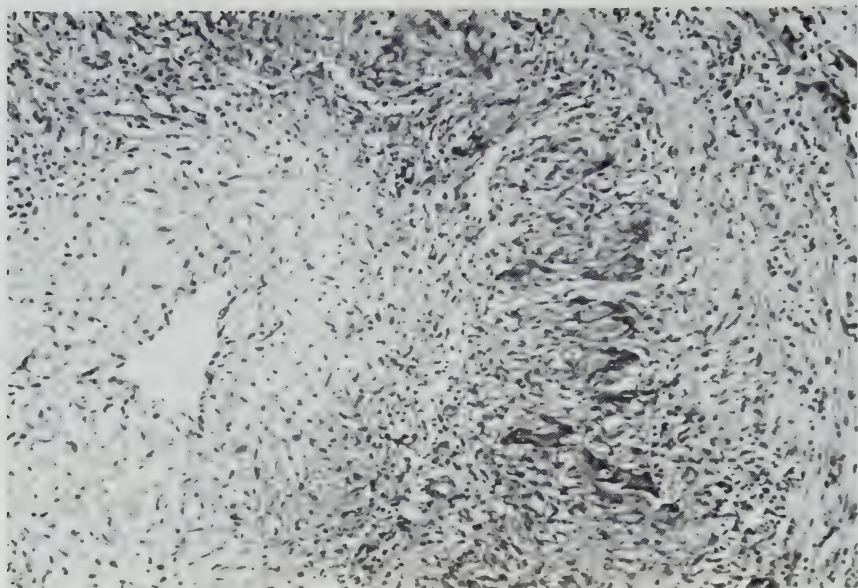


Fig. III:1.

Case 1. Biopsy from temporal artery. Florid inflammation with general oedema, numerous giant cells and diffuse lymphocyte infiltration. Htx — eos. x 300.

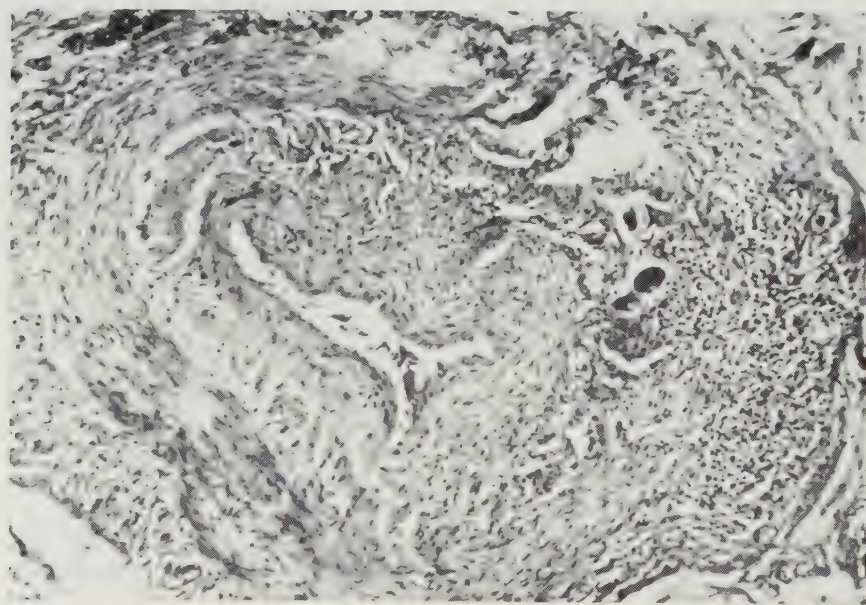


Fig. III:2.

Case 1. Temporal artery at necropsy 8 months later. Pronounced narrowing with intimal fibrosis, destruction of elastic lamella, round cell accumulation in adventitia and media and a couple of giant cells. Htx — eos. x 300.

arteries. More pronounced inflammation of the distal
Cause of death: Arteritis with gangrene of the leg.
part of the right femoral artery (Figs. III:6, 7).

Case 3, a man, born in 1890.— In 1959 examined because of raised E.S.R., 9, 68, 43 mm/l hr. Complained of pain in the neck extending up over the ears. On admission E.S.R. 100 mm/l hr, nephropathy with mild uraemia. — In 1962 heart symptoms, E.S.R. 3, 7, 20 mm/l hr. Moderately increased serum creatinine. Soon recovered. — Admitted to hospital in March 1972 with chest pain and respiratory distress, died 11 days later.

Necropsy: Aorta markedly widened from the valves to the descending part, and somewhat tortuous. Increasing arteriosclerosis distally, below the origin of the renal arteries an aneurysm the size of a tennis ball, bulging backward and filled with a stratified thrombus. Generalised arteriosclerosis with old, small brain infarctions, constricting coronary sclerosis with scattered fibrous scars in the myocardium. — Minimal pulmonary emboli. — Signs of heart failure with pleural effusion and general congestion.

Microscopical findings: Arteritis of the large arteries. Cause of death: Generalised arteriosclerosis. Arteritis with aortic dilatation.

Case 4, a woman, born in 1886. — In 1958 she had increasing headache of changing localization, sometimes "lightning" sensations in the eyes, associated with the headache. E.S.R. 69 mm/l hr, WR neg. — A benign hypertension was diagnosed with mild enlargement of the heart and a somewhat widened and tortuous aorta. She was sent home with digitalis and diuretics. — Some months later shoulder pain with restricted movements. E.S.R. 55 mm/l hr. — In the spring of 1960 marked restriction of movements and weakness of shoulder and neck muscles. Fever of 38°C. — In March, 1960, she could not get out of bed without aid. E.S.R. 100 mm/l hr. Increasing loss of weight. — In the summer of 1961 she complained of dizziness. Towards the autumn marked tenderness of the temples, biopsy showed temporal arteritis. She was treated with steroids with marked clinical improvement, E.S.R. decreasing from 106 — 30 mm/l hr. Steroid-treatment was continued until 1967. — In 1967 spells of unconsciousness, bradycardia was found and pace-maker-treatment started. — In December, 1972, she fell acutely ill with cardiac decompensation and died.

Necropsy: Aorta moderately widened in arch and descending part, fairly pronounced atheromatosis, mild wrinkling between plaques. Fist-sized malignant glioma in right parietooccipital region. Aspiration of

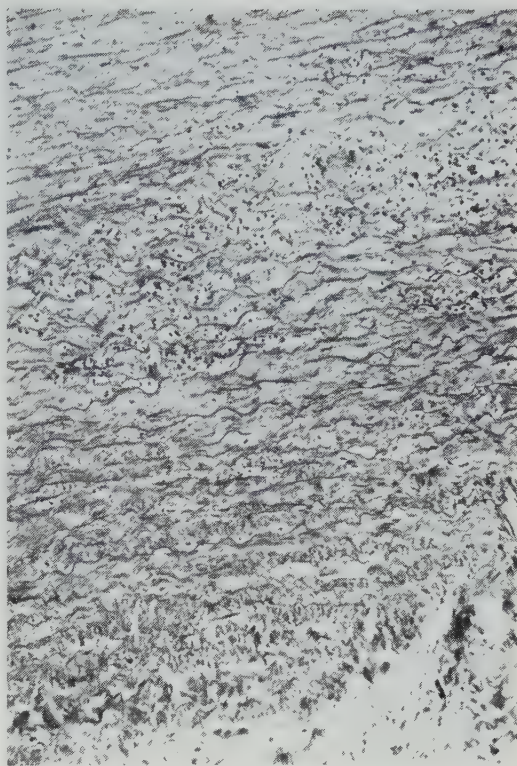


Fig. III:3.

Case 1. Thoracic aorta. Intima above, adventitia below. Oedematous zone in outer media with diffuse lymphocyte infiltration, one giant cell. Htx — eos. x 300.

foreign material in lungs with foreign body granulomas and widespread bronchopneumoniae.

Microscopical findings: Arteritic changes in large vessels. (Figs. III:8, 9).

Cause of death: Cerebral tumour.

Case 5, a woman, born in 1900. — Rheumatic fever with affection of the heart in childhood, since when irregular cardiac rhythm on exercise, no other symptoms reported. Admitted to hospital in 1963 because of dizziness and headache with impairment of vision of right eye. A homonymous upper quadrant anopsia which was regarded as a sequela after retinal embolism. Roentgen examination showed enlargement of the heart with configuration as in mitral stenosis. She was sent home improved and anticoagulant therapy was instituted. — In 1965 the blood pressure was found to be high. — In 1972 the patient suddenly fell ill with retrosternal pain and died from cardiogenic



Fig. III:4.

Case 1. Subclavian artery. Moderately thickened, oedematous intima above with blood-filled capillaries near internal elastic membrane. Oedema of outer media with fragmentation of elastic lamellae and round cell infiltration. Htx — eos. x 75.

shock twelve hours after admission to hospital.

Necropsy: The aorta showed general wrinkling of the intima, moderate arteriosclerosis with white-yellow raised plaques. — A transverse rupture was found immediately above the aortic valves with haemopericard and haemo-mediastinum. — Moderate mitral stenosis and insufficiency. — Signs of heart failure with generalised acute congestion. — Old cerebral infarction in left occipital lobe.

Microscopical findings: Patchy arteritic changes in aorta.

Cause of death: Aortic rupture because of arteritis.

Case 6, a woman, born in 1893. — Known hypertension for several years. In 1967 she had temporal arteritis verified by biopsy, and was treated with steroids. — The following years she had increasing uraemia and angina pectoris of varying severity. In 1971 she had a myocardial infarct, and died in increasing oliguria with oedema.

Necropsy: Aorta of normal width, generalised wrinkling of the intima, distally increasing pale yellow lipid plaques. — Signs of hypertension with enlargement of the heart and nephrosclerosis. Extensive fresh infarction in anterior wall of left ventricle and septum, signs of circulatory failure with pulmonary oedema and general congestion.

Microscopical findings: Arteritis of chronic type.

Cause of death: Myocardial infarction.

Case 7, a woman, born in 1887. — Cholecystectomy in 1959. Left-sided fracture of the femoral neck in 1970. Treated because of hypertension since unknown time. — In October, 1970, acute swelling and tenderness in the temples bilaterally and headache localised to the back of the head. Sudden left-sided impairment of vision. Biopsy showed temporal arteritis. E.S.R. 60 mm/l hr. — Treated with steroids, which resulted in general improvement and decreasing E.S.R. — Suddenly fell ill with fever and respiratory distress in July 1971, chemotherapy-treatment had no

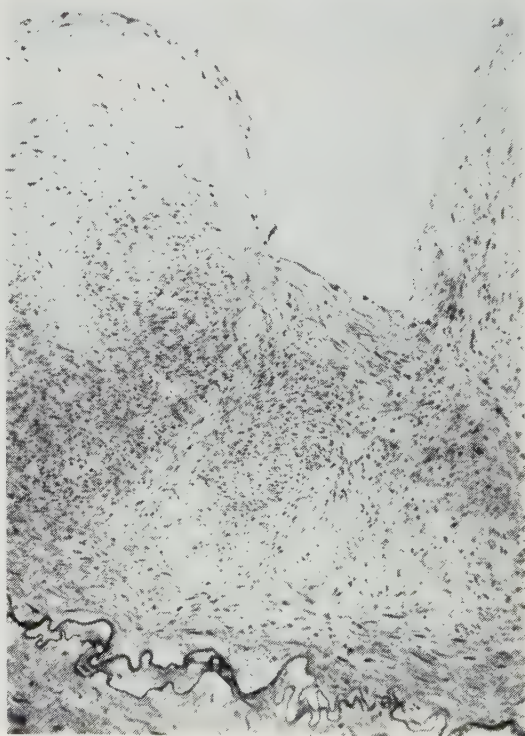


Fig. III:5.

Case 1. Deep femoral artery. Irregular, cellular, oedematous thickening of intima. Preserved internal elastic lamina at lower margin. Htx — eos. x 75.

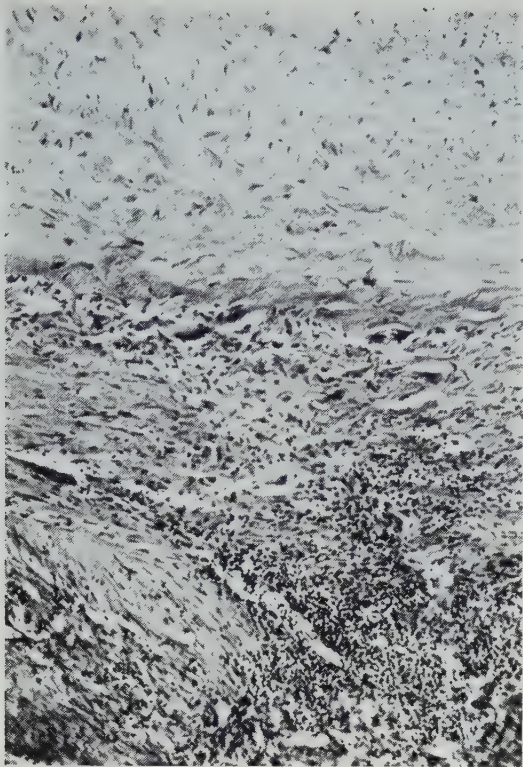


Fig. III:6.

Case 2. Femoral artery. Intima, above, thickened and cellular. Multinucleated giant cells at internal elastic membrane. In media, below, dense lymphocytic infiltrate and fragmentation of muscle bundles. Htx — eos. x 120.

notable effect on body temperature. One week later she was admitted as an emergency in a very poor condition, and died the same day.

Necropsy: Pronounced atheromatosis of aorta. Coronary sclerosis with old scars after infarctions in the myocardium of the left ventricle and several small, more recent infarcts. Signs of cardiac failure with bilateral hydrothorax, pulmonary oedema and general congestion.

Microscopical findings: Widespread arteritic changes in aorta and other large arteries.

Cause of death: Coronary sclerosis. Small myocardial infarcts.

Case 8, a man, born in 1899. — Arthritis symptoms after tonsillitis in 1940. Since the same time pulmonary tuberculosis that run a fluctuating course, sometimes cavernous. He also had the diagnosis of

schizophrenia. — From the 1950s cardiac murmur, interpreted as aortic stenosis and insufficiency. Admitted to hospital with pulmonary oedema in August 1972 and soon died.

Necropsy: Pronounced dilatation of ascending aorta and arch with thick and irregular intima. Distally, moderate arteriosclerosis with scattered fibrous intimal plaques in abdominal aorta. — Stenosis and insufficiency of aortic ostium, signs of heart failure with generalised congestion. — Healed left-sided pulmonary tuberculosis with fibrous obliteration of left pleura.

Microscopical findings: Arteritic changes in some sections (Fig. III:10).

Cause of death: Insufficiency of aortic valves + aortitis.

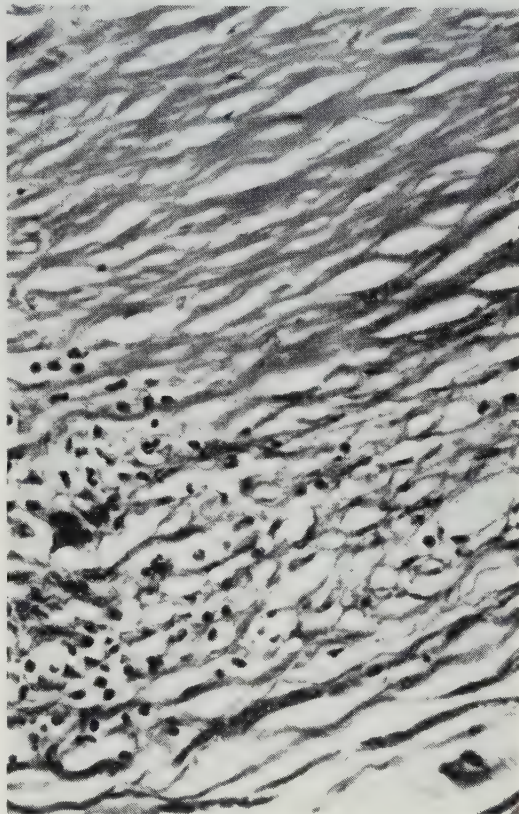


Fig. III:7.

Case 2. Coronary artery. Outer part of media, intima above. Necrotic part of thickened intima and media up to the right, around a break collections of lymphocytes, one giant cell. Htx — eos. x 120.

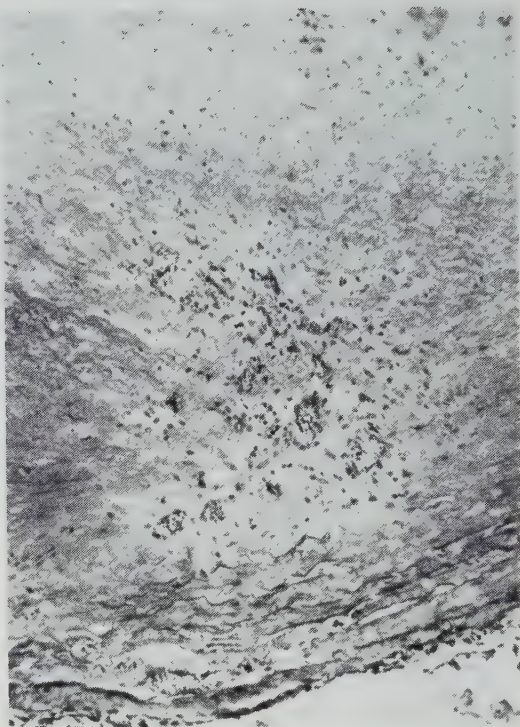


Fig. III:8 + 9.

Case 4. Two adjacent parts of subclavian artery with thick, cellular intima above, media below with remnants of necrotic tissue with dissolved elastic lamellae and organising, fibrous tissue with capillaries in between. Some preserved elastic lamellae of outer media at lower margin. Htx — eos. x 120.

Case 9, a woman, born in 1949.— At 3 years of age she developed rheumatoid arthritis, which produced deformities and bound the patient to a wheel-chair. Cardiac murmur discovered early, was interpreted as aortic stenosis and insufficiency. — Prolonged thrombocytopenia, occasionally with gastric bleeding. — In 1970 admitted to hospital because of urinary tract infection and pneumonia, improved after chemotherapy. — In January, 1971, rapidly increasing shortness of breath and oedema of lower legs, died in respiratory failure. E.S.R. 15-65-77-34 mm/1 hr.

Necropsy: Proximally, the aorta showed a pale, yellow smooth intima with single, pinhead-sized lipid plaques. From 2 cm proximally to the origin of the renal arteries and distally to the bifurcation the intima was greyish, thickened and wrinkled. — Widespread articular changes with ankylosis and deformities of the hands, knees and feet, pronounced spinal deformity with narrowing of the thoracic cage. — Chronic endocarditis with fibrosis of the mitral and aortic valves. — Widespread, fresh and old haemorrhages in

the lungs, probably due to thrombocytopenia. — Moderate deposition of amyloid in kidneys, spleen, pancreas and liver.

Microscopical findings: Arteritis in aortic arch with its branches and in the distal aorta. (Fig. III:11, 12). Cause of death: Pulmonary haemorrhages.

Case 10, a man, born in 1915. — Since some years morbus Bechterew, not very severe. Angina pectoris, in 1962 operated upon, a flap from diaphragm was brought into the left part of the pericardium. — In 1971 suddenly severely ill with pulmonary oedema and died.

Necropsy: Aorta of normal width, its wall rather thin, intima thickened and wrinkled. Moderate atheromatosis. — Severe coronary sclerosis with narrowing. Small fibrous scars in myocardium, streaks of acute infarction.

Microscopical findings: Small areas of acute arteritis. (Fig. III:13, 14, 15).

Cause of death: Myocardial infarction.

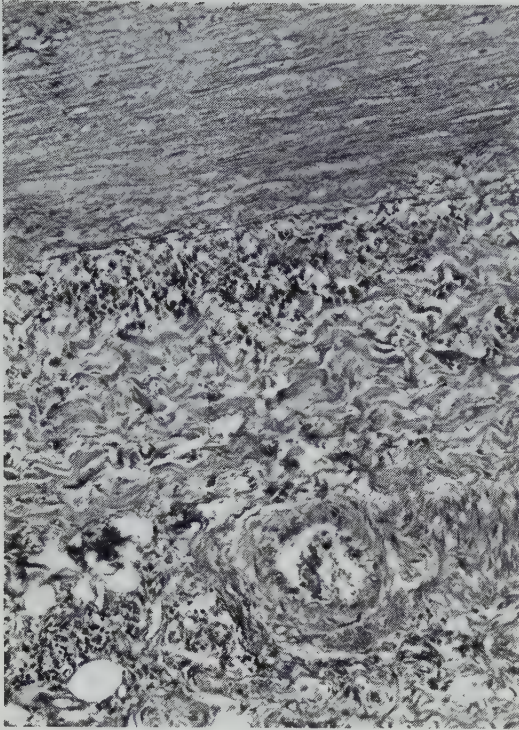


Fig. III:10.

Case 8. Arcus aortae. Normal media in the upper part. Dense fibrosis of adventitia below, a rather wide arteriole of normal anatomy. At the border between media and adventitia and in the adventitial fibrous tissue infiltrates of plasma cells and lymphocytes. Htx — eos. x 300.

Case 11, a woman, born in 1897. — Rheumatic fever at 15 years of age. In the 1940s she had joint symptoms. — In 1960 and 1964 she was cared for because of cardiac symptoms, - widening of the aorta was detected with calcification of the wall, as in syphilitic aortitis. WR and T.P.I. were positive as were Meinicke and Kline. WR and Meinicke in cerebrospinal fluid negative. — Treatment with penicillin. — Periods of cardiac insufficiency in association with infections in 1968 and 1969. — Admitted to hospital in May, 1970, because of cardiac insufficiency, refractory to treatment, gradually deteriorated and died.

Necropsy: Aorta of normal width with rigid wall. From the ascending part and distally widespread calcifications in the intima, which was partly detached. Generalised, fine longitudinal wrinkling in less calcified areas. — Aortic valve insufficiency with

left ventricular hypertrophy and generalised enlargement of the heart. Widespread bilateral bronchopneumoniae.

Microscopical findings: Adventitial fibrosis, possibly sequelae after arteritis.

Cause of death: Insufficiencia valvulae aortae.

Case 12, a woman, born in 1891. — In 1948 admitted to hospital because of syphilis with positive WR. — Since the 1950s swelling of the legs in the evening. — Acute attack of chest pain in November, 1969, infarction suspected. Examination revealed murmurs as in aortic stenosis and insufficiency. WR and T.P.I. positive. — Discharged improved after 20 days. — On a few occasions in 1970 she had incompensation. — In February, 1971, she was acutely ill with increasing shortness of breath. Died after four days from increasing cardiac insufficiency.



Fig. III:11.

Case 9. Abdominal aorta. Irregularly thickened intima above, oedematous tissue with few, elongated nuclei, some smooth muscle cells, some fibroblasts. Media below with irregularity of elastic lamellae, some penetrating capillaries and small areas of fibrous tissue. Htx — eos. x 75.



Fig. III:12.

Case 9. Proximal part of carotid artery. Preserved elastic media above. Dense fibrosis of adventitia with sparse, small nuclei, in the lower part. Htx — eos. x 300.

Necropsy: Generalised, pronounced arteriosclerosis of aorta, which was of normal width. Insufficiency and stenosis of aortic ostium, enlargement of the left ventricle. — Signs of heart failure with pulmonary oedema, hydrothorax and generalised congestion.

Microscopical findings: Mild adventitial fibrosis with small round cell infiltrates.

Cause of death: Stenosis et insufficiencia valvulae aortae.

Case 13, a woman, born in 1898. — In 1913 operated upon because of thyrotoxic goiter. — In 1919 gonorrheal salpingitis and syphilitic infection. Treated 1919 — 1922 and 1928 — 1929. 1948 and 1961 WR negative. — In 1970 the patient was admitted to hospital for investigation of chest pain. X-ray examination revealed moderate enlargement of the heart, fusiform dilatation of the ascending aorta as in syphilitic aortitis. — Admitted in March, 1972, with right-sided abdominal pain and diarrhoea. Suddenly died while in hospital.

Necropsy: Moderate dilatation of aorta and rupture of ascending aorta with haemopericardium. — Pronounced atheromatosis of the aorta with signs of atheroma emboli with multiple scars in the kidneys. Signs of cardiac failure with pulmonary oedema and general congestion.

Microscopical findings: Arteritic changes, mainly masked by atheroma.

Cause of death: Aortitis, aortic rupture.

Case 14, a man, born in 1892. — Symptoms of bronchitis from the 1940s. — From about 1967 increased shortness of breath, treated with digitalis and diuretics. — Chronic, very productive cough. According to the patient, he had for many years had an E.S.R. of about 70 mm/l hr. He had not been investigated for the raised E.S.R. — In 1971 WR and T.P.I. proved positive. — In the spring of 1972 he was admitted to hospital because of increasing respiratory distress and cardiac insufficiency. Died after gradual deterioration.



Fig. III:13.

Case 10. Aorta near diaphragm. Intima above. In outer part of media oedema with round cell infiltration. Htx — eos. x 120.

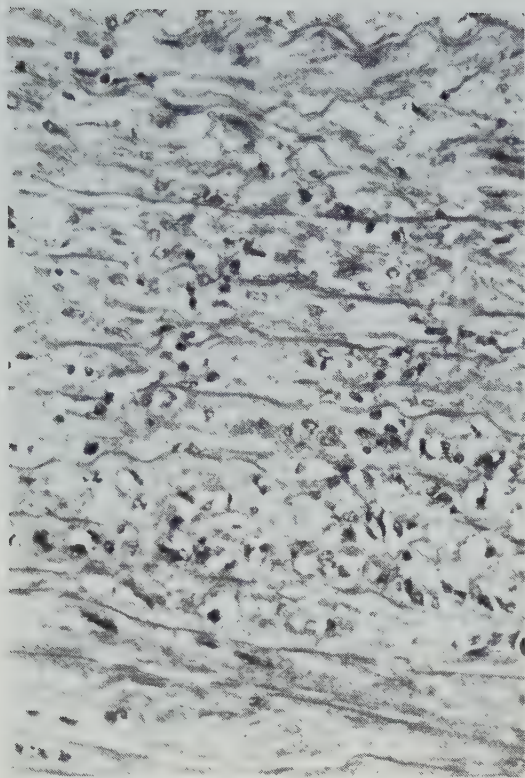


Fig. III:14.
Detail of former picture. Oedema of media with lymphocytes. Htx — eos. x 300.

Necropsy: The aorta was notably wide, especially the ascending part and the arch. The intima was diffusely wrinkled, mild arteriosclerosis with fibrous plaques. — Bronchiectasia with chronic and acute bronchitis.

Microscopical findings: Adventitial fibrosis, which may have been sequelae after arteritis. No active arteritis. (Figs. III:16, 17).

Cause of death: Chronic bronchitis.

Case 15, a man, born in 1904. — Syphilis in 1932, local treatment. In 1948 fever therapy. — In 1972 WR neg., Kline pos., FTA pos. — He suddenly fell ill in November, 1972, with chest pain, and died ten days later of myocardial infarction.

Necropsy: Ascending aorta moderately widened, severe atheromatosis with large calcified plaques, increasing distally. — Large infarction in apex of left ventricle with endomural thrombi.

Microscopical findings: Pronounced atheromatosis, areas of adventitial fibrosis.

Cause of death: Myocardial infarction.

Case 16, a woman, born in 1937. — An aunt had died from cardiac failure at 16—17 years of age. — In 1940 admitted to hospital for investigation of valvular disease, which could, however, not be verified. — In 1947 she was re-investigated and again no diagnosis could be made with certainty, but she probably had mitral valve affection. — In 1960 she was again investigated. This time a widened or lengthened aorta was found, a pulsating vascular tumour or aneurysm in the left carotid area and a systolic murmur in the left I:3 — I:4. Because of her physical constitution her condition was diagnosed as Marfan's syndrome. — In November, 1960, she was delivered of a healthy child by Caesarean section. — In January, 1961, she suddenly fell ill with chest pain which radiated up towards the cheeks and down the back.

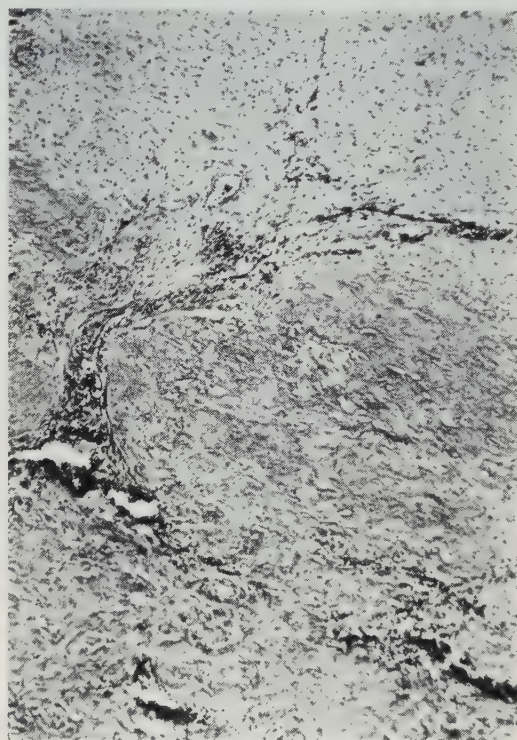


Fig. III:15.
Case 10. Brachiocephalic trunk. Media, in the middle part, defective with penetrating, blood-filled capillaries, surrounded by some histiocytes, plasma cells and lymphocytes. In the upper part intima with rather cellular fibrous tissue without inflammation, in the lower part adventitia with dense fibrosis. Some lymphocytes around blood-filled capillaries. Htx — eos. x 75.



Fig. III:16.

Case 14. Brachiocephalic trunk. Outer part of media with preserved structure above, one small penetrating capillary at the upper margin. Severely thickened, fibrous adventitia with a small, rather thick-walled artery. Htx — eos. x 75.

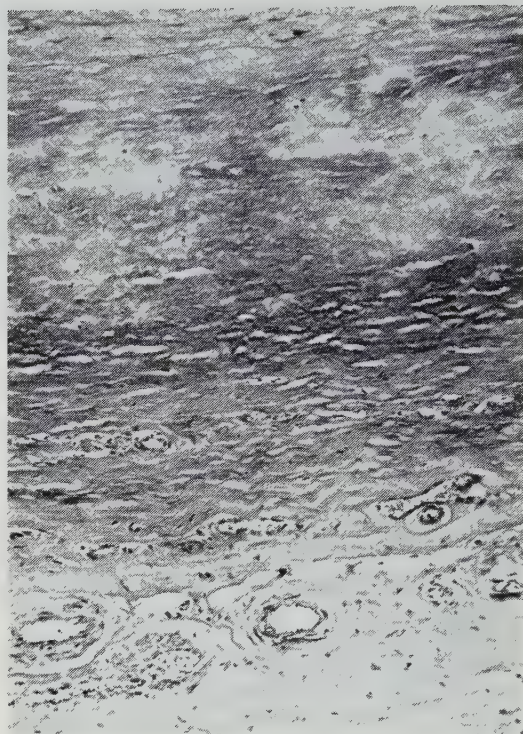


Fig. III:17.

Case 14. Subclavian artery. Outer part of media above, adventitia below. Slight fibrosis of the latter with thick-walled, small artery to the left and wide, thin-walled venules. Irregular necrosis of media without inflammatory reaction. Htx — eos. x 120.

Loud diastolic murmur, interpreted as aortic insufficiency. She was treated with hypothermia, tracheostomy, respirator but died from circulatory failure the following day.

Necropsy: Thickened aortic valves, aortic rupture 2,5 cm above the ostium and a dissecting aneurysm in the right carotid artery, the thoracic and abdominal aorta and proximal iliac arteries with intimal ruptures bilaterally 2—5 cm from the bifurcation. — The signs of Marfan's syndrome were typical physical constitution, arachno-dactylia, vertebral scoliosis, visceral ptosis.

Microscopical findings: Splitting up of media with spaces of varying size filled with metachromatic material. No inflammatory changes.

Cause of death: Medionecrosis aortae with rupture and dissecting aneurysm.

RESULTS

MACROSCOPIC FINDINGS

Arteritis in polymyalgia arteritica (7 cases), rheumatic valvular disease (1), rheumatoid arthritis (1) and spondylarthritis anchylopoetica (1 case)

The aortic valves were described as somewhat thickened in four cases (5, 8, 9 and 10). Slight insufficiency of the aortic valves was found in case 9.

Widening of the aorta from just above the valves and extending down towards the abdo-

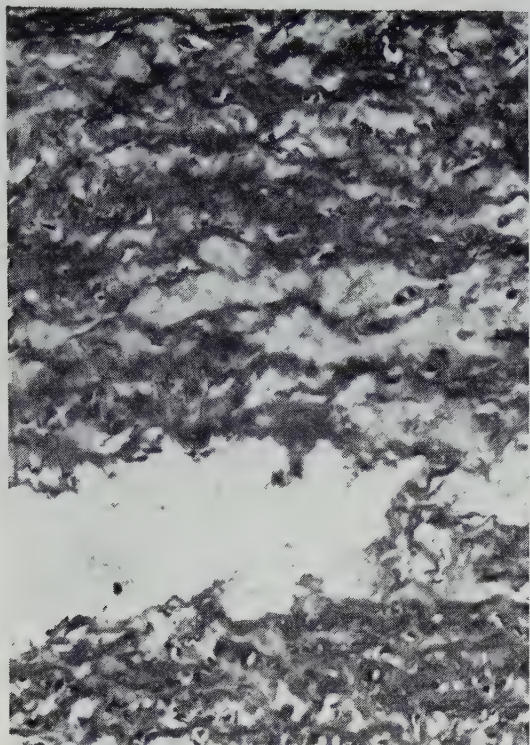


Fig. III:18.

Case 16. Aorta ascendens. Outer part of media with end of dissecting aneurysm. Loosening of medial structure with lacunae, containing metachromatic material. Htx — eos. x 300.

minial aorta, with an aneurysm the size of a tennis-ball below the origin of the renal arteries had been observed in case 3.

Pronounced dilatation of the ascending aorta towards the aortic arch was noted in case 8, and a moderate dilatation of the aortic arch and descending aorta in case 4.

A mild to moderate general wrinkling and thickening of the intima of the aorta was found in 6 cases (1, 3, 4, 5, 6 and 10). In all of these cases there was mild to moderate arteriosclerosis with fibrous plaques and some calcifications distally. — A remarkable thickening of the intima with raised yellow and greyish areas in

the region from 2 cm proximally to the origin of the renal arteries to the bifurcation was described in case 9. In the aortic arch and the descending aorta there were only scattered pin-head-sized, soft yellow atheromatous plaques.

The axillary arteries were slightly narrowed in case 1; in the others were no changes in the large arterial branches from the aortic arch.

Rupture of the wall of the aorta just above the valves with dissection down towards the pericardium and up into the carotid to the base of the skull was found in case 5.

Two patients had died from complications of arteritis, one (case 5) from aortic rupture and the other (case 8) from insufficiency of the aortic valve.

Syphilitic aortitis (5 cases)

Dilatation of the aortic ostium with fibrous thickening of the valves was noted in case 11, stenosis of the ostium as well as insufficiency with thickened valves was noted in case 12. The other three patients (13, 14 and 15) had thin and smooth aortic valves with ostia of normal width.

Aortic rupture was noted in 2 cases; in No 16 2.5 cm above the ostium and in No 13 immediately proximal to the origin of the brachiocephal trunk.

There was general widening of the aortic arch in 3 cases (14, 15 and 16).

Pronounced atheromatosis with calcifications was observed in 4 cases (11, 12, 13 and 15). It began already proximally in the ascending aorta and was roughly equally pronounced down in the abdominal aorta.

MICROSCOPIC FINDINGS

Arteritis in polymyalgia arteritica

In three cases in an early stage (cases 1, 2, 7 with 8, 2 and 9 months' history, respectively) a layer in the outer media showed oedema with general splitting of the elastic lamellae and

deposition of lymphocytes and plasma cells, single polymorphonuclear leukocytes. Intimal thickenings in the form of cushion-like projections were seen, mostly in thin vessels, with or without medial changes. No changes were observed in the vasa vasorum. — Later in the course necroses appeared in the media, often in parts of it, mainly the outermost part with collapse and destruction of the elastic lamellae. Around breaks in necrotic media were connective tissue scars with or without chronic inflammation. Two cases (4, 6) with prolonged steroid treatment showed only small defects in the medial layer, which had been replaced by connective tissue with thin capillaries and without inflammatory cells. — Mild adventitial fibrosis was sometimes seen but no changes in the vasa vasorum.

Arteritis in "rheumatic" diseases

Partly similar changes were seen (case 8). In a young woman (case 9) large areas showed collapse of the media with necrosis, but no breaks of the necrotic elastic lamellae. Prominent intimal thickening, partly in the form of highly cellular cushion-like formations bulging into the lumen, partly with connective tissue, poor in cells with spaces after dissolved fat and ingrowing capillaries, changes here suggesting arteriosclerosis (but observe the patient's age, 22 years, where arteriosclerosis is, as a rule, less pronounced).

Syphilitic aortitis

Three cases (12, 13, 14) showed massive adventitial fibrosis poor in cells. The vasa vasorum were clearly thickened with narrow lumina. Lymphocyte infiltration was occasionally seen around these vessels, but most often there was no notable inflammatory reaction. In two (11, 15) of five cases there were extremely mild changes with very little adven-

titial fibrosis in single sections and moderate thickening of the walls in the vasa vasorum.

Medionecrosis aortae

In a woman with Marfan's syndrome, aged 24 years, splitting of the medial layer without certain necrosis of the elastic lamellae and without inflammatory reaction was found. In addition, there was fresh bleeding into the outer medial layer or between the media and the adventitia. There was relatively pronounced metachromasia of the intima and media.

LOCALISATION OF THE CHANGES **Arteritis in polymyalgia arteritica and** **"rheumatic" diseases**

All 10 cases showed changes in some part of the aorta, in 5 of them in the major part of the aorta (1, 2, 3, 6 and 7); in others, in minor areas in the ascending, descending or abdominal aorta. All cases showed changes in some parts of the subclavian arteries, 7 also in some part of the carotid arteries. Arteritis was noted in 4 cases in the arteries of the lower limbs.

Syphilitic aortitis

In 3 cases there were changes in the aortic arch and proximally in its large branches (12, 13 and 14). In two cases changes were found only in a limited part of the descending aorta (11, 15), in the latter the brachiocephalic trunk was also involved.

Medionecrosis aortae

Loosening of the media with metachromatic material was noted in all sections examined. Dissection within the aorta, right carotid artery and proximal leg arteries is marked in the diagram.

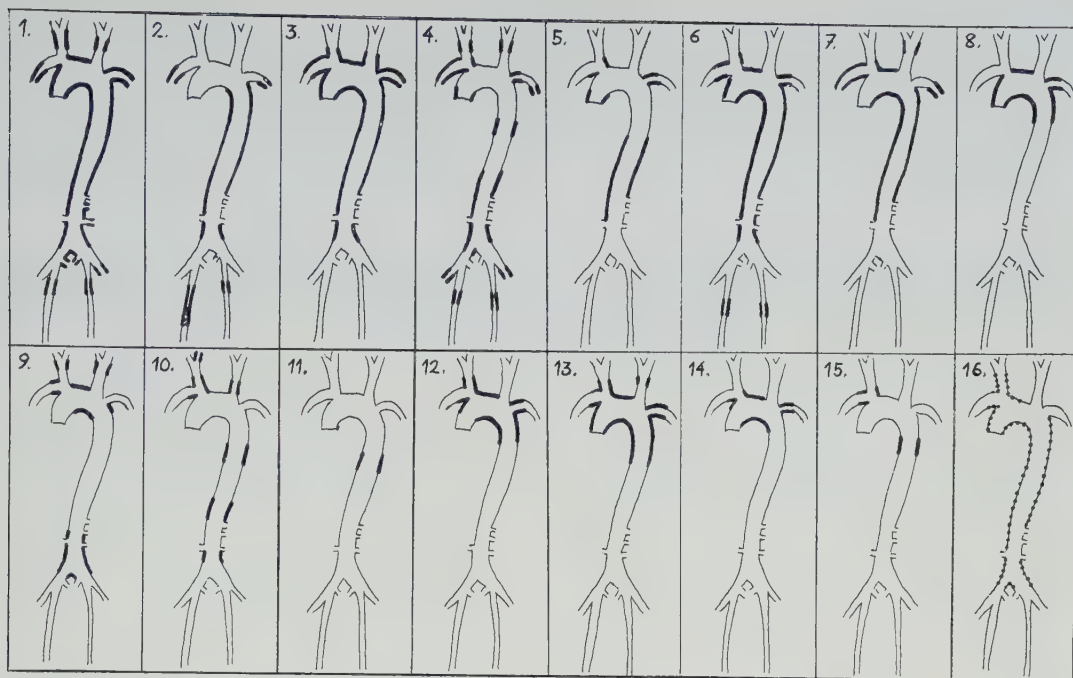


Fig. III:19.

Diagrams of findings in cases 1—16. Arteritis marked by thick contours, thrombosis by hatching. In case 16 marks dissection.

COURSE OF DISEASE AND CAUSES OF DEATH

Arteritis in polymyalgia arteritica and "rheumatic" diseases

Three patients (2, 5, 8) died from complications of arteritis with cardiac insufficiency and leg gangrene, aortic rupture and insufficiency of the aortic valve because of dilatation of the aorta, respectively. In two cases, (1, 3) the patients died from cardiac insufficiency combined with possibly changed resistance and dilatation of the aorta. Two patients (6, 10) had extensive myocardial infarction, which could explain the deaths. One patient (4) died from a tumour, one (7) from coronary sclerosis with minor infarction. One patient (9), a young woman with juvenile rheumatoid arthritis, had widespread changes in organs, joints and arteries, but the direct cause of death was pulmonary haemorrhage on the

basis of chronic thrombocytopenia, possibly related to the basic disease or to the treatment given.

Syphilitic aortitis

Two patients with known syphilitic infection died from aortic valve disease and in these the syphilitic injuries might have contributed to death. One patient (13) died suddenly from aortic rupture, which could be explained by aortitis with possibly secondary pronounced arteriosclerosis. It might be questioned whether this was of the type seen in polymyalgia arteritica. Two patients (14, 15) died of causes probably not related to the arterial changes, *viz.* chronic bronchitis and a large recent myocardial infarction.

The patient with Marfan's syndrome (16) died from aortic rupture on the basis of medionecrosis and dissecting aneurysm.

Table III:2

Nr	Temp		Coronary			Pulm	Coeliac	Mes. sup.	Renal		Cer.	Organs
	R	L	R	Ld	Lc				R	L		
1	+	+	+	+	+	—	—	+	—	—	+	—
2	+	+	+	—	+	..	..	..	..	..	..	—
3	..	..	..	..	..	..	..	..	..	..	..	—
4	+	+	—	—	—	—	—	—	—	—	..	—
5	..	..	..	..	..	..	..	..	—	..	..	—
6	+	+	+	—	—	..	—	—	—	—	—	—
7	+	+	..	..	..	..	..	—	—	—	..	—
8	—	—	—	—	—	—	—	—	—	—	..	—
9	..	..	..	..	..	..	..	..	..	..	..	..
10	..	..	..	..	..	..	—	—	—	—	—	—
11	..	..	..	..	..	..	—	—	—	—	—	—
12	..	..	..	..	..	..	—	—	—	—	..	—
13	..	..	..	..	..	..	..	..	—	—	..	—
14	..	..	..	..	..	..	..	..	..	..	—	—
15	..	..	..	..	..	..	—	—	—	—	—	—
16	..	..	..	..	..	..	..	..	..	..	..	—

Arteries, not included in diagrams. Temporal arteries (right and left), coronary arteries (right, left descending and left circumflex), pulmonary, coeliac, superior mesenteric, renal (right and left), basal cerebral arteries. Organs (lungs, kidneys, liver, spleen, myocardium, vertebral bone marrow).

+ arteritis or sequelae after arteritis

— no arteritis

... no investigation

CONCLUDING REMARKS

The studies confirmed the findings in the previous work (I) on the type and localisation of arteritic changes in polymyalgia arteritica, including cases with the clinical picture of “temporal arteritis”. The latter could preferably be incorporated in “general arteritis” or polymyalgia arteritica. — The 22-year old girl with juvenile rheumatoid arthritis had arterial lesions which closely resembled those in the 17-year old girl with Takayasu’s disease (described in paper I). In this and two other patients with “rheumatic” affections the arteritis did not differ significantly from arteritis in polymyalgia arteritica.

Syphilitic arteritis showed other macro-

and microscopic changes; two of five patients had very mild lesions in the aorta, the other three arteritis localised above all to the aortic arch and the proximal parts of the large branches close to the aortic arch. In medianecrosis aortae, exemplified by Marfan’s syndrome, loosening and degenerative changes of the media were seen but without inflammatory reaction.

Patients with polymyalgia arteritica are affected late in life and die in advanced age (72—85 years), but similar arterial changes were seen in a 22-year old girl and in two men in their 50s with “rheumatic” diseases. — The primary syphilitic infection usually occurs in early adult age but arterial lesions may persist throughout life.

TEMPORAL ARTERITIS IN A LARGE NECROPSY SERIES (PAPER II)

INTRODUCTION

In 1962—1963 the town of Malmö had a population of 250,000 inhabitants. Since the town has only one general hospital, one hospital for chronic and one for mental diseases, and since all are served by one department of pathology, the possibilities of estimating the frequency of a given disease are good. About 65 % of all people dying in the town during the period were necropsied (98 % of patients dying in hospital). It was therefore considered possible by systematically collecting temporal arteries at necropsy and examining them microscopically to get an opinion of the frequency of temporal arteritis in the population. The material consisted of 1,097 cases.

MATERIAL AND METHODS

During one year specimens of the temporal arteries were obtained at necropsy of all adults. In 763 cases (70 %) pieces of arteries were obtained from both sides, in 280 cases (26 %) from one side. One to three transverse sections from a 1 cm piece of the artery was examined.

RESULTS

Twelve cases showed arterial changes in the form of intimal thickening with fibrosis and narrowing of the lumen, capillary ingrowth

in the media or adventitia, adventitial fibrosis or deposition of round cells in the adventitia. In two of the twelve cases temporal arteritis had been confirmed by biopsy two years before death, seven had had headache, muscle pain or general malaise suggesting polymyalgia arteritica between 1 to 14 years before death. In the remaining three cases no previous disease could be traced. The diffuse symptoms in the seven patients could be explained by the arterial changes observed post mortem but only two of twelve had clinically diagnosed disease. — The frequency of temporal arteritis in the necropsy material was about 1 %.

From 1960 to 1970 about eleven biopsy specimens from the temporal arteries were examined per year at the Department of Pathology and in five arteritis was found. If biopsies were performed on most patients with suspected temporal arteritis the disease would be diagnosed clinically in about 4 per 100,000 inhabitants per year and verified by biopsy in 2 per 100,000. The frequency found in the necropsy material was thus much higher than that detected *intra vitam*. — The changes persist for a long time and are of relatively characteristic type. — In three cases material from the aorta showed signs of arteritis or sequelae after arteritis. This is in agreement with the assumption that temporal arteritis is a component of a

more widespread arterial disease. It appears, however, to have a "benign" course and not to affect the duration of survival, since the causes of death in these patients were the same as otherwise in the necropsy series in Malmö.

CONCLUDING REMARKS

Lesions in the temporal arteries of recent or old arteritis were found in 1 0/0 of the patients on

systematic study of one year's necropsy material. Two of the twelve patients had had temporal arteritis, verified by biopsy, two years before death. Seven had had diffuse symptoms, which might have been polymyalgia arteritica one to fourteen years before death. In three cases there were no notices of former disease.—Sequelae after arteritis were seen as narrowing of the artery with fibrosis of intima and adventitia. The media was partly destroyed with fibrous scarring.

CHAPTER V

RETROSPECTIVE INVESTIGATION OF A NECROPSY MATERIAL

INTRODUCTION

At routine necropsy the aorta and the large vessels are examined macroscopically and the degree and extent of arteriosclerosis described. As a rule, microscopic examination is made only when gross findings are remarkable. One can therefore hardly expect all cases of arteritis, which often produces only slight gross changes, to be discovered at routine examination. A possible exception is syphilitic arteritis, which is known to occur in a certain percentage of cases of syphilis and where the aorta might be studied more closely. Besides

for cases with clearly diagnosed arteritis or aortitis the registers were therefore searched for complications apt to occur in arteritis such as aneurysms, ruptures and dissection.

MATERIAL AND METHODS

During the period 1957—1971 20,591 necropsies of live-borns (10,484 males and 10,107 females) of various ages had been performed at the Institute of Pathology in Malmö. The age distribution is given in Fig. V:1. Gross changes seen at necropsy were noted in a protocol and a varying amount of tissue was col-

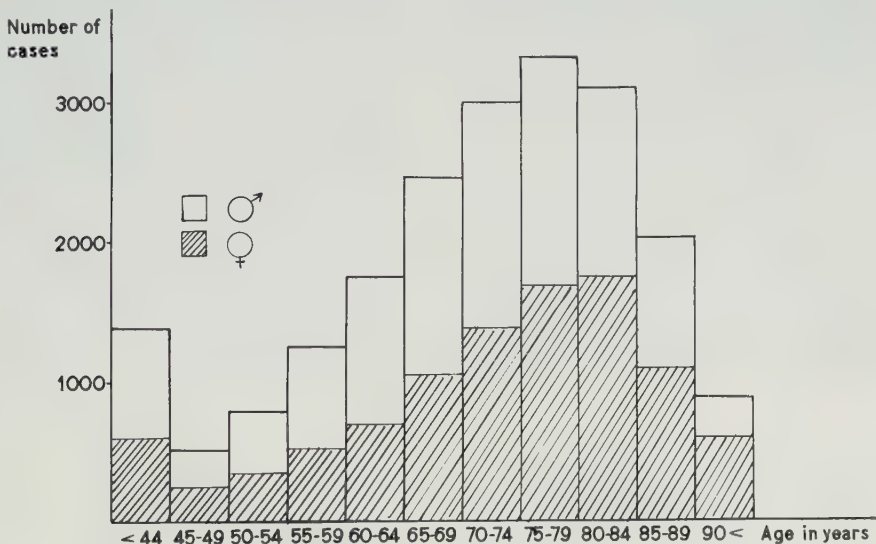


Fig. V:1.

Age distribution in the Malmö necropsy material 1957—1971.

lected for histological examination. After microscopical examination the pathologic-anatomical diagnosis was made and relevant diagnoses were entered under the necropsy number in a register. The investigation included all cases registered as giant-cell aortitis, temporal arteritis, non-specific arterial inflammation, polyarteritis nodosa, syphilis, rheumatic arterial disease, medionecrosis aortae and dissecting aneurysm, rupture and aneurysm of aorta. The protocols were examined, and in those cases where material from the large arteries was available, the sections were examined. In

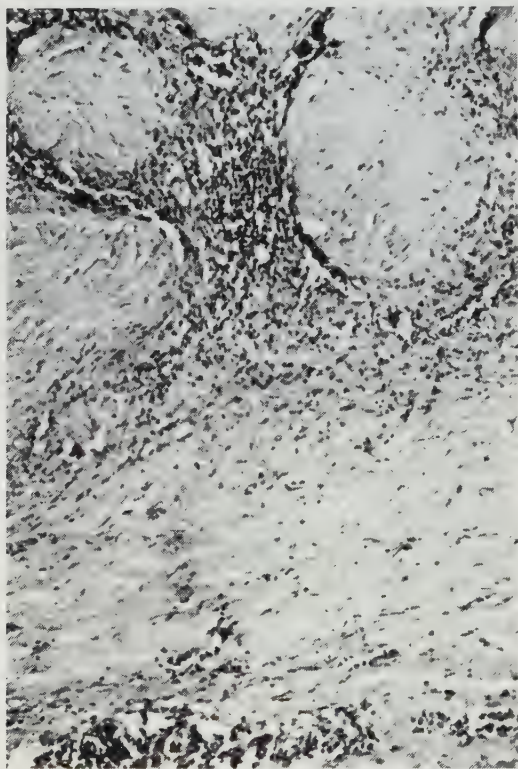


Fig. V:2.

Case V:1. Wall of aneurysm of aortic arch. Outer part of arterial wall, intima above, adventitia below. Necrosis of media with widespread destruction of elastic lamellae, which are replaced by dense fibrous tissue. In lacunae in this fibrotic tissue capillaries, surrounded by numerous plasma cells and lymphocytes. Htx — eos. x 120.

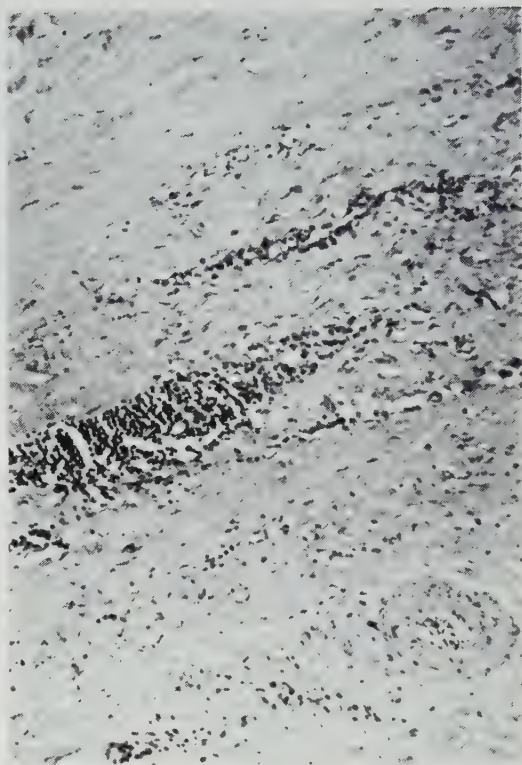


Fig. V:3.

Case V:1. Another part of the same aneurysm wall. Medial structure above replaced by dense fibrous tissue with lymphocytes and plasma cells around capillaries. Fibrosis of adventitia below with thick-walled, narrow arteriole. Htx — eos. x 300.

some cases additional staining for elastin and for metachromasia (toluidine-blue) was made. The histological sections were examined without knowledge of the gross findings or clinical histories. Data about the patients and the findings were entered on needle cards for the further processing of the material. — As the collection of this retrospective necropsy material included the year 1971, some of the cases, studied systematically (Chapter III) as well as some of the cases, found in the prospective studies (VI) were included. A few cases appeared in all three materials. They were, however, found independently in the different surveys.

Illustrative case reports

Case V:1, a woman, born in 1896. No previous diseases. Fracture of the femoral neck in 1967, examination revealed positive WR, and she was treated with penicillin. In 1968 roentgenography revealed a large aneurysm of the ascending aorta and arch, which gradually increased in size. Died suddenly in 1970. *Necropsy* showed marked widening of the ascending aorta, whose wall was not thicker than paper, moderate widening of the arch, and distally thereto another, widened segment with a fist-sized aneurysm filled with stratified, firm, yellow-brown thrombic masses. The lower thoracic aorta was of normal width. In the distal part of the aneurysm a 3 cm long rupture was found with widespread haemorrhages in the left lung and in the left pleural space. *Microscopy* showed syphilitic aortitis (Fig.

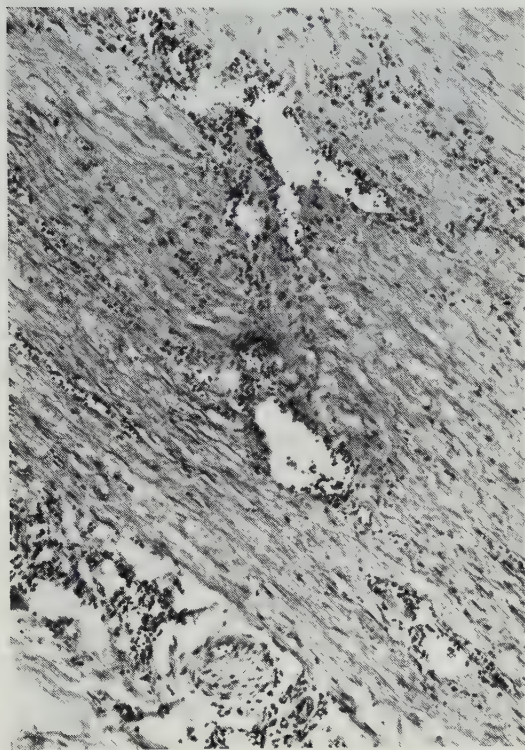


Fig. V:4.

Case V:2. Arcus aortae. Outer part of media above, adventitia at the lower left hand corner with thick-walled arteriole. Around wide capillaries, penetrating into media, accumulations of plasma cells and lymphocytes. Elastic staining of the same artery shows preserved elastic tissue of media. Htx — eos, x 75.

V:2, 3). Cause of death: aneurysmal rupture, syphilitic aortitis.

Case V:2, a woman, born in 1890. Probably rheumatic fever in 1917. Angina pectoris from 1958, myocardial infarction in 1962, signs of aortic valve disease, positive WR and TPI. Cardiac insufficiency from 1963. Progressive deterioration, death in 1964. *Necropsy* showed aortic dilatation immediately after the ostium decreasing in the arch. The intima was diffusely thickened with mother-of-pearl-like surface, abundant yellow-white atheromatous plaques. The origins of the coronary arteries and the large branches from the aortic arch were constricted. The aortic valves were diffusely thickened with signs of insufficiency and the heart was enlarged. There was a massive pulmonary oedema. The main branches of the pulmonary artery were filled with thromboemboli. *Microscopy* showed syphilitic aortitis (Fig V:4). Cause of death: Pulmonary embolism.

Case V:3, a man, born in 1895. Syphilis during youth, treated in 1919. Disability pension in 1950 because of hypertension. Admitted to hospital in 1959 because of cardiac insufficiency, improved during the following years. In 1965 he deteriorated progressively and died from pulmonary oedema. *Necropsy* showed moderate widening of the aortic arch with almost confluent, pale-yellow, partly calcified atheromatous plaques. Moderate widening of thoracic aorta, distally increasing atheromatosis with calcifications. Pronounced left ventricular hypertrophy, massive coronary sclerosis, fibrous scars in the myocardium. Signs of heart failure with pulmonary oedema. *Microscopy* showed syphilitic aortitis (Fig. V:5). Cause of death: Cor hypertonicum incompensatum.

Case V:4, a woman, born in 1909. Previously healthy. In July, 1969, sudden epistaxis, hypertension was found and treated medicamentally. In November, 1970, nosebleeding recurred. While cleaning a carpet in December, 1971, she suddenly fell ill with severe breast pain. Admitted to hospital and died within a few hours. *Necropsy* showed general widening of the aorta from the origin to the arch. A 35 mm long oblique rupture 10 mm above the valves was found with dissection down towards the valves and via the arcus down into the thoracic aorta to the level of the diaphragm. The intima was wrinkled with raised yellow-white plaques. Moderate left-sided cardiac hypertrophy. Pulmonary oedema. *Microscopy* showed arteritis of the type seen in polymyalgia arteritica. Cause of death: Aortic rupture due to aortitis.

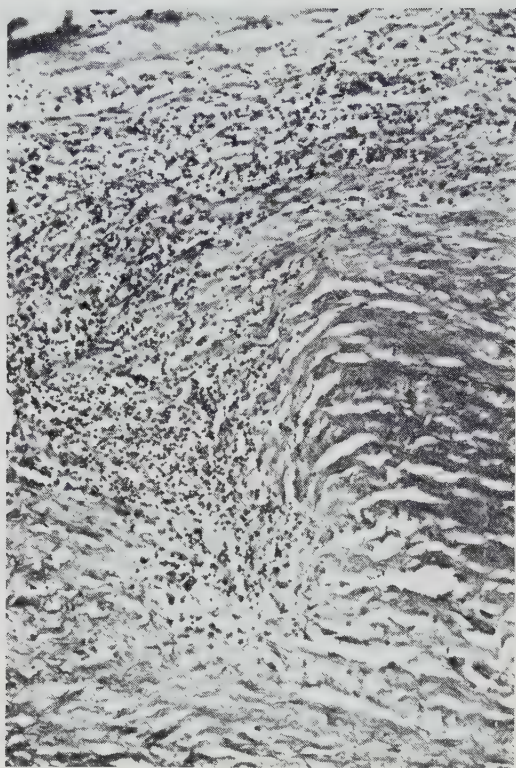


Fig. V:5.

Case V:3. Unspecified part of aorta. Intima above. Break in media with wide, blood-filled capillary at left margin, numerous plasma cells and lymphocytes. No discernible nuclei in probably necrotic part of media to the right, elastic staining, however, shows preserved structure of elastic lamellae. Htx — eos. x 75.

Case V:5, a man, born in 1901. Symptoms of prostatism in the 1960s, prostatectomy, later on urinary tract infection, which improved after chemotherapy. E.S.R. 55—80 mm/l hr. — Sought advice in September, 1968, because of acute symptoms with pain in upper part of abdomen, forehead and temporal headache. E.S.R. 110 mm/l hr. Good general condition. No treatment. — Five weeks later sudden weakness, transient loss of consciousness. Admitted to hospital moribund and died the following day. *Necropsy* showed an aorta of normal width with moderate arteriosclerosis, increasing distally. Left ventricular hypertrophy. Fresh haemorrhage in pons. *Microscopy* showed temporal arteritis, no specimen from aorta. Similar inflammation was seen in small arte-

ries in the organs, the picture was that of polyarteritis nodosa. Cause of death: Cerebral haemorrhage.

Case V:6, a woman, born in 1896. 1919 treated because of syphilis. — 1966 admitted as an emergency with pain in the right half of the abdomen and radiating up towards the breast. Suddenly died after admission. *Necropsy* showed aortic dilatation immediately after the origin, about 13 cm in diameter, decreasing towards the arcus. Two centimeters above the valves was an 8 cm long transverse rupture with dissecting haemorrhage along the arch, descending and abdominal aorta to 10 cm distally to the bifurcation. *Microscopy* showed pronounced metachromasia in the media of the aorta, no arteritis. Cause of death: Aortic rupture, medionecrosis aortae idiopathica.

RESULTS

Arterial changes were noted in 658 cases. They could be divided into 6 groups according to the gross and microscopic changes. Some of the diagnoses must be based on microscopic findings, while arteriosclerosis, for example, is diagnosed mainly macroscopically. The arteriosclerosis group therefore contained cases that could not be referred to the other more specific groups. The diagnoses were arteriosclerosis, arteritis, syphilis, medionecrosis aortae and polyarteritis nodosa. The numbers of cases with and without microscopic examination are given in Table 1. The basis of the diagnosis of arteritis and the preceding symptoms in these cases are discussed below. In medionecrosis aortae there is a loosening of the arterial wall with rupture and dissection; these cases are discovered mainly by the complications that may arise. To a certain extent it is a rest diagnosis for cases not showing changes of arteritis. In most cases recorded as syphilitic arteritis the diagnosis was based on microscopic examination. True arteritis was found in only a part of the cases, which is discussed below. — Polyarteritis nodosa involves mainly vessels with a caliber up to a few millimeters, and in only about

one third of the cases was material available from the large arteries. The diagnosis needs not be discussed further here. — Two thirds of the cases, classified as arteriosclerosis had not been examined histologically. In those cases where material was available, microscopic examination had to distinguish between changes of arteritis and changes that could not be classified as such and were therefore ascribed to arteriosclerosis.

AGE DISTRIBUTION

The age distribution of the various diagnosis groups is given in 5-year classes in Fig. V:6. The patients with arteritis are found in

slightly higher age classes than those with other diagnoses. Especially polyarteritis nodosa shows a wide range of variation from young years to high age. The difference between the cases of arteritis and the large group of arteriosclerosis is less certain.

MAIN CAUSE OF DEATH

The effect of the arterial disease on the patient's health and survival is reflected in the causes of death in the various groups. The relative number of complications was largest for medionecrosis aortae, followed by polyarteritis nodosa, arteritis, syphilis and arteriosclerosis, in the order given (Table 2).

Table V:1

Diagnosis	Histology	No histology	Total
Arteriosclerosis	116	318	434
Arteritis	79	—	79
Syphilis	63	3	66
Medionecr. aortae	40	—	40
Polyart. nodosa	9	30	39
Total	307	351	658

Microscopical study of material from the large arteries, according to diagnosis groups.

Table V:2

MAIN CAUSE OF DEATH									
Diagnosis	Cardiovasc.		Tumour		Infection + other		"Complication"		Total
	Nr	%	Nr	%	Nr	%	Nr	%	
Arteriosclerosis	167	39	76	18	118	27	73	17	434
Arteritis	27	34	11	14	12	15	29	37	79
Syphilis	18	29	13	20	22	33	13	20	66
Medionecrosis aortae	2	5	1	3	4	10	33	83	40
Polyarteritis nodosa	3	8	2	5	10	26	24	62	39
Total	217		103		166		172		658

Main cause of death in different diagnosis groups.

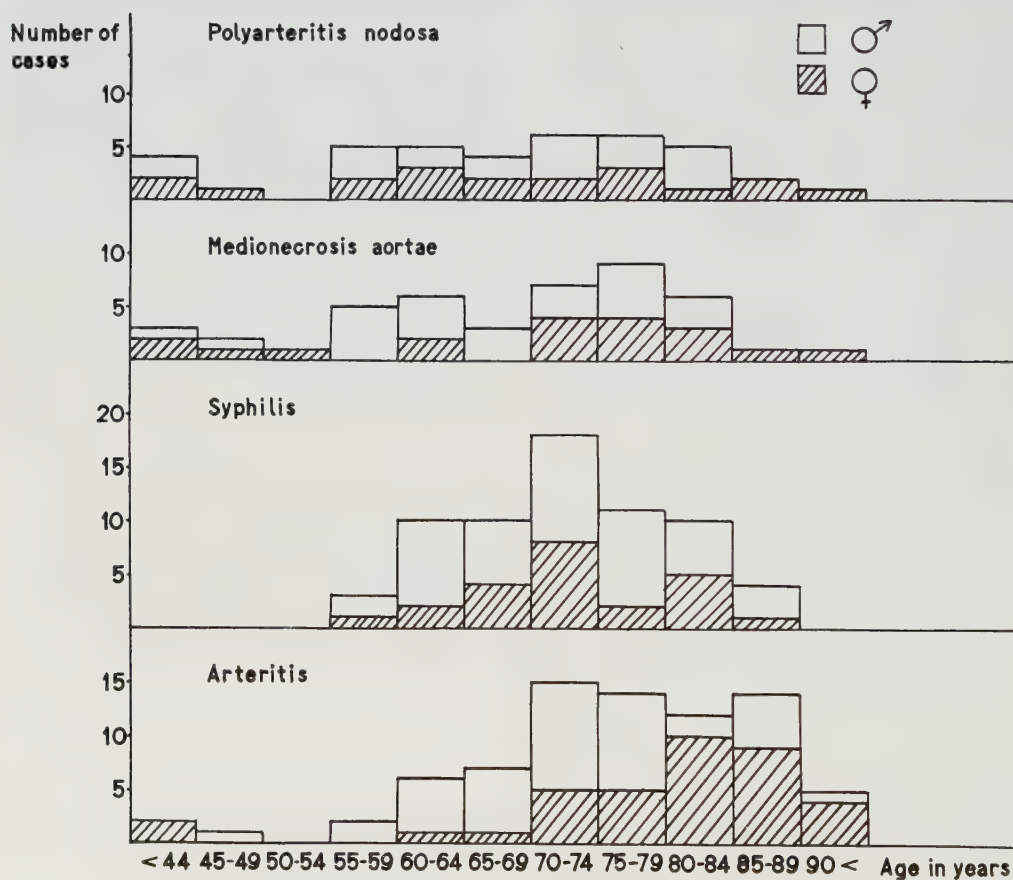
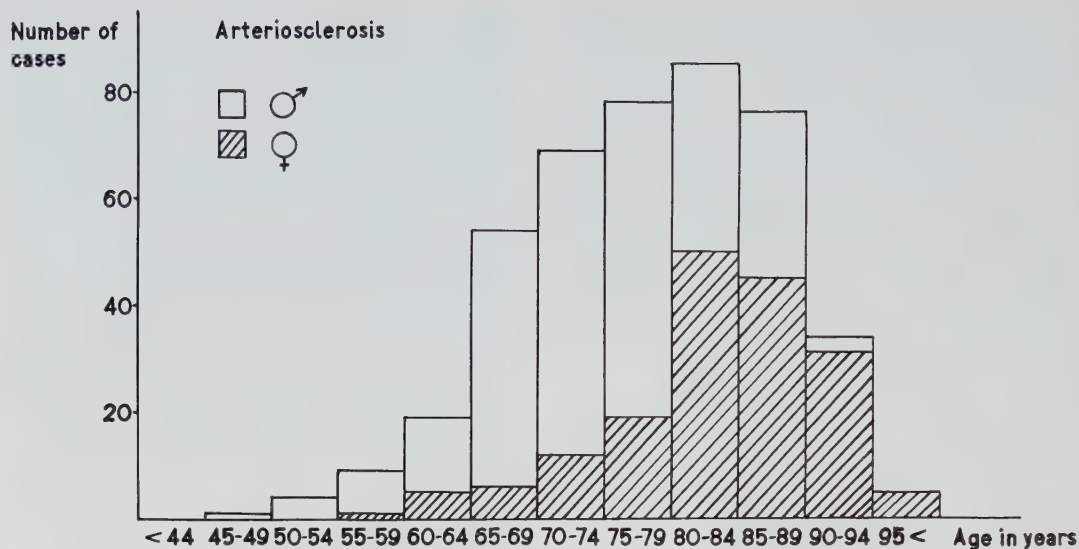


Fig. V:6.

Age distribution of cases in different diagnosis groups.

AORTIC ANEURYSMS

The site and size of aneurysms of the aorta were noted and are given in Fig. 4. The arteriosclerotic aneurysms were about 10 times more common than aneurysms in association with arteritis and syphilis.

Of all together 443 aortic aneurysms, 377 (85 %) were due to arteriosclerosis, 36 (8 %) to syphilis and 30 (7 %) to arteritis. 354 aneurysms were situated in the abdominal aorta and of these, 325 (92 %) were arteriosclerotic, 12 (3 %) syphilitic and 17 (5 %) arteritic. The remaining part of the aorta contained 85 aneurysms, 50 (59 %) of which were of atheromatous nature, 22 (26 %) syphilitic and 13 (15 %) arteritic.

In arteriosclerosis aneurysms of the abdominal aorta were predominant. Uncomplicated aneurysms that were discovered incidentally at necropsy were about 2—5 cm in diameter. Ruptured arteriosclerotic aneurysms were significantly larger, about 10—15 cm in diameter, and these, too, were most common in the abdominal aorta. 272 patients had a single aneurysm and 32 multiple aneurysms.

Of 66 patients with a diagnosis of syphilis 23 (35 %) had aneurysms, which were more spread and involved the arch as well as the thoracic and abdominal aorta. The aneurysms were relatively larger than the arteriosclerotic aneurysms. Rupture had occurred in 15 %.

Eleven (14 %) of 79 cases of arteritis had 21 aneurysms, distributed roughly in the same way as the arteriosclerotic aneurysms.

OTHER AORTIC CHANGES THAN ANEURYSM

General widening of the aorta

Aortic widening was observed in 63 (14 %) of 434 cases with arteriosclerosis. Of 79 patients with arteritis, 20 (25 %) showed general widening of the aorta; 11, mainly of the ascending part; and 8, of the ascending part,

the arch and the descending thoracic part. One case showed a widening of the arch. In 18 (27 %) of 66 cases with syphilis the aorta was widened; in 9 the ascending part was involved; in 4, the ascending part and the arch; in four, the arch and in one, the descending thoracic part.

Rupture without aneurysm

Of the patients with arteriosclerosis 18 (4.1 %) died of aortic rupture without any known aneurysm. Thirteen patients with arteritis (16.5 %) died of such aortic rupture and none with syphilis.

FREQUENCY OF AORTIC CHANGES

The annual number of cases with different diagnoses is given in Table 4. The total frequency of arteriosclerotic aneurysms was 2 %, of syphilis 0.3 %, medionecrosis aortae 0.2 % and polyarteritis nodosa 0.2 %. The frequency of arteritis in this retrospective investigation was 0.4 %. The increase during the last years in the number of arteritis cases may reflect an increasing recent interest with greater awareness of changes suggestive of arteritis. Other variations were inconstant and are probably due to an increase in the number of necropsies.

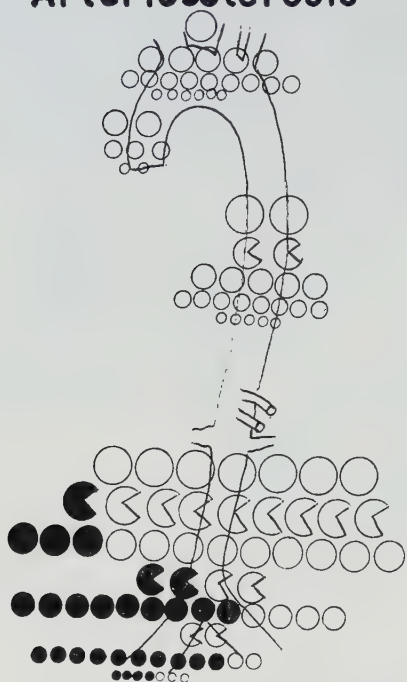
CHANGES OBSERVED IN THE VARIOUS DIAGNOSIS GROUPS

Arteriosclerosis

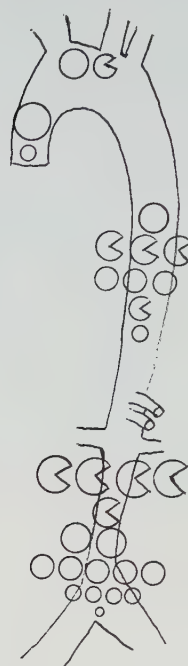
(The investigation embraced only aneurysms recorded).

Several of these had been macroscopically classified as arteriosclerotic aneurysms, only in one third of the cases was material available for microscopic checking. The severity of the microscopic changes varied; the intima was thickened with structureless, amorphous masses, sometimes spaces after dissolved fat;

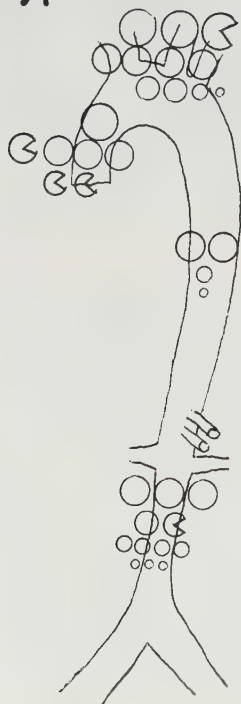
Arteriosclerosis



Arteritis



Syphilis



Diameter

○	15 cm	●	x 10
○	10 "	●	"
○	5 "	●	"
○	2 "	●	"
○	1 "	●	"

◐ Rupture ◑ "

Fig. V:7.

Diagrams of aortic aneurysms of different etiology. Localisation in ascending aorta, arcus, descending thoracic and abdominal aorta. Size and complications (rupture).

Table V:3

Diagnosis Site of changes	Diffuse widening	Non aneurysmal rupture	Other or no macr. change
Arteriosclerosis	63	18	—
Ascendens	2 {	11	
Arcus		2	
Descendens thoracica	6 {	4	
Abdominal		1	
Arteritis	20	13	26 (intimal thickening)
Ascendens	8 {	10	
Arcus		1	
Descendens thoracica		2	
Abdominal			
Syphilis	18		21 (no change)
Ascendens	4 {	9	
Arcus		4	
Descendens thoracica	1		
Abdominal			

Macroscopical changes other than aneurysm in the aorta.

sometimes, the inner parts of the media were involved. There was, however, little or no inflammatory reaction, no circumscribed medial necroses or other specific changes that could be classified as arteritis. Whether arteritis was nevertheless masked by the arteriosclerotic lesions is discussed below. The major part of these patients died from diseases unrelated to the aortic changes, but some 20 % from “complications”, mainly rupture of aneurysms. Since arteriosclerosis is so very common, the incidence of aneurysms was not impressive and complications in the form of rupture were very uncommon compared with the number of fatal complications of arteritis.

Arteritis

This group included typical arteritic changes, but varying from active relatively recent changes to sequelae after arteritis in patients where previous arteritis was less certain. The distribution of the cases according to more or less typical arterial changes and their relation to anamnestic data is given in Table 5. Pronounced arterial changes were somewhat more common in cases with previous positive biopsy or clinical history (suggesting polymyalgia arteritica) than in patients without evidence of earlier disease of polymyalgic type. More than one third of the patients had died from complications of arteritis. The distribution of

Table V:4

Year	DIAGNOSIS					
	Number necropsied	Arterio- sclerosis	Arteritis	Syphilis	Medio- necrosis	Polyart. nodosa
1957	899	5	—	3	—	—
1958	865	15	4	4	—	2
1959	1022	23	2	5	1	4
1960	1123	16	1	7	1	3
1961	1150	18	3	2	1	2
1962	1232	27	5	4	—	3
1963	1336	21	6	1	3	2
1964	1347	22	7	10	3	3
1965	1369	21	2	5	1	2
1966	1508	35	6	7	4	4
1967	1626	35	4	4	6	2
1968	1711	32	12	4	5	1
1969	1841	51	9	2	6	3
1970	1750	51	9	5	3	7
1971	1812	62	9	3	6	1
Summary	20.591	434	79	66	40	39

Number of cases per year in different diagnosis groups.

Table V:5

Anamnesis	Arteritis	"Healed arteritis"	Possibly arteritis	Specimen not diagnostic	Total
Temporal artery biopsy positive	6	6	1	1	14
Polymyalgia arteritica	7	9	7	1	24
No information about polymyalgia	3	22	16	—	41
Total	16	37	24	2	79

Anamnestic data in cases with arteritis.

aneurysms in the aorta differed barely from that of the arteriosclerotic aneurysms. It should, however, be observed that a dilatation of the ascending aorta was much more common in cases with arteritis. In 29 (37 %) of the cases there was no dilatation or aneurysms, the gross changes were described as intimal thickening and wrinkling with a varying admixture of arteriosclerotic changes.

Syphilitic aortitis

Most cases had been examined histologically, probably mainly because of the earlier infection, which was noted in the patients' histories in all cases. Most had positive serological tests, some had previously had such which, however, had proved negative at later control. Of the 66 patients with a diagnosis of syphilis, 23 (35 %) had typical microscopic arterial changes with thickening of the adventitia and thickened vasa vasorum, sequelae after syphilitic arteritis. Twenty-one (32 %) had changes which might perhaps be sequelae after arteritis and 17 (26 %) no clear-cut arteritis. In 3 cases no material for microscopic examination was available. One patient had aortic rupture with dissecting aneurysm of the type seen in medionecrosis aortae, no certain syphilitic arteritis. In one case, (V:1), there were widespread arteritic changes of active type with giant cells. This was probably an acute arteritis, not related to syphilis.

Medionecrosis aortae

Pathognomonic changes are barely found in the aortic wall. There is a more or less pronounced loosening of the media with the occurrence

of metachromatic material, changes which, however, to a certain extent occur normally in advanced age. To this group were assigned cases with dissecting aneurysm, with splitting of the media but no inflammatory changes. One case with dissection and inflammation was regarded as arteritis.

Polyarteritis nodosa

Material from the large arteries was available in 9 of 39 cases. No arteritic changes were observed.

CONCLUDING REMARKS

In 20,591 necropsies from Malmö during the years 1957—1971 diseases of the large arteries (unspecific inflammation, temporal arteritis, giant cell arteritis, polyarteritis nodosa, syphilis, rheumatoid arteritis, medionecrosis aortae and dissecting aneurysm, rupture and aneurysm) were registered in 658 cases. In 307 cases pieces from the aorta or other large arteries were available for microscopical evaluation. — 434 cases were classified as arteriosclerosis, 79 as arteritis, 66 as syphilis, 40 as medionecrosis aortae and 39 as polyarteritis nodosa. — In 38 of 79 cases of arteritis (florid or old, according to histological changes of the large arteries) the patient had had temporal arteritis or polymyalgia arteritica a varying time before death. Thirty-seven per cent of patients with signs of arteritis died from aortic rupture or other complication, 17 % of the patients with arteriosclerotic aneurysms and 20 % of those with syphilis.

PROSPECTIVE STUDY OF AORTIC AND OF AORTIC + TEMPORAL ARTERY CHANGES, RESPECTIVELY

INTRODUCTION

As a supplement to the earlier investigation of temporal arteritis in a necropsy series, examination of aortic changes was started. This examination was later extended to include a material with tissue specimens from both aorta and temporal arteries.

MATERIAL AND METHODS

A. From June 1, to November 30, 1971, a transverse section of the ascending aorta 5 cm above the aortic valves was obtained from all adults, necropsied at the Department of Pathology, Malmö General Hospital. The pieces were fixed in neutralised formalin, divided into two or three shorter pieces, embedded in paraffin, sectioned and stained with haematoxylin-eosin. Such pieces of the aorta were obtained at 560 autopsies. The age distribution of the material is given in Fig. VI:1.

B. From December 1, 1971 to May 31, 1972 pieces of tissue from the aorta and from the temporal arteries were obtained from all adults necropsied at Malmö General Hospital and at Värnhem hospital (hospital for chronic diseases). Specimens of the temporal arteries were obtained in the way described previously (II) from the inner side of the scalp in as-

sociation with the opening of the skull. A piece of aorta was obtained from the ascending aorta about 5 cm above the valves and one roughly at the level of the diaphragm. The pieces were processed in the same way as in series A. — Such material was obtained at 389 necropsies. The age distribution is given in Fig. VI:2 (A shift to the right in this diagram compared with the previous is due to the fact that the patients who had died in Värnhem's hospital belonged to significantly higher age groups).

At microscopic examination aortitis was diagnosed when, according to the findings in Paper I, there was a diffuse lymphocyte infiltration in the media with splitting of the elastic lamellae (acute arteritis) or delimited medial necroses with thickening of the elastic lamellae, sometimes with breaks with round cell infiltration, possibly multinucleated giant cells (less recent arteritis). Adventitial fibrosis was also noted as were changes in the vasa vasorum.

Temporal arteritis was diagnosed according to the same criteria as in Paper II according to the findings of intimal fibrosis, vascularisation of the wall, destruction of the elastic membrane with accumulations of round cells and maybe giant cells, and adventitial fibrosis.

Sequelae after syphilitic aortitis were seen as a fibrous thickening of the adventitia with

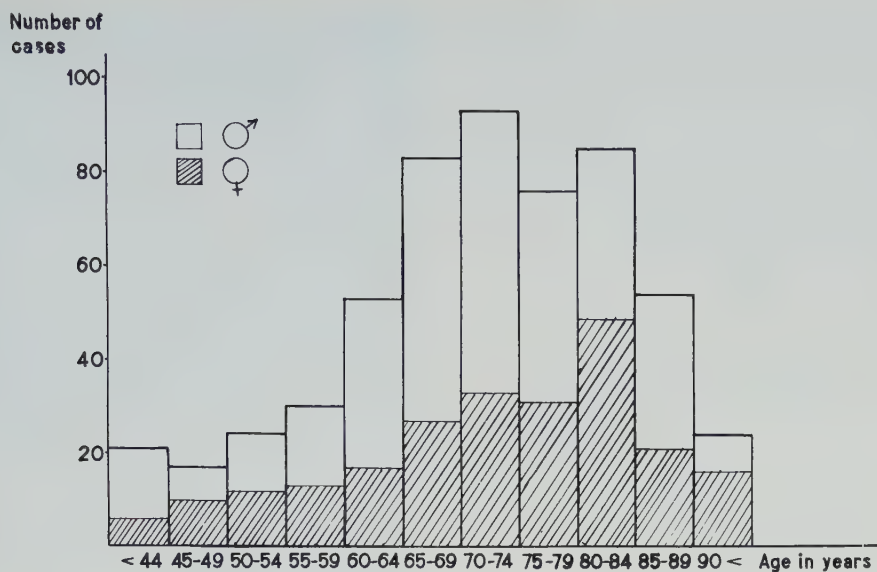


Fig. VI:1.

Age distribution in series A (one piece from aorta 1/6—30/11 1971).

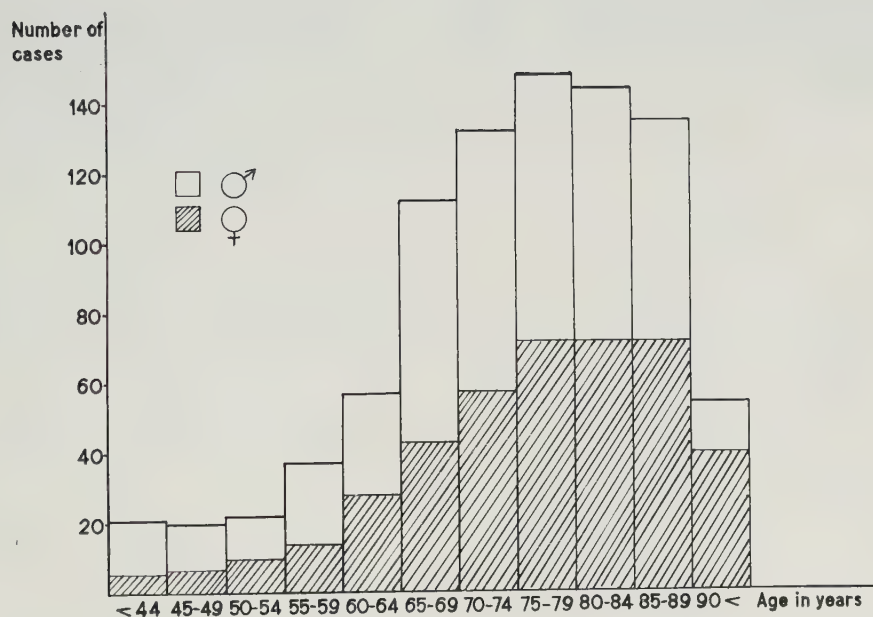


Fig. VI:2.

Age distribution in series B (temporal arteries + two pieces from aorta 1/12 1971—31/5 1972).

thick-walled vasa vasorum, which often had very narrow lumina. There was a varying extent of round cell infiltration. In some cases streaks from the adventitia into the media were seen, where the elastic lamellae were destroyed and fibrous tissue with wide, thin-walled capillaries was found. The extent of arteriosclerotic changes varied.

Atheromatosis appeared as intimal thickening with structureless material or clefts after disappeared fatty material. Adjacent to marked and greatly thickened intimal plaques necrosis was sometimes seen in the media, immediately under the intima. Small streaks of lymphocytes could be found, an occasional multinucleated giant cell. There were no necrotic parts in the deeper media and no breaks with dense round cell infiltrates.

At examination of the aorta notes were made also of "medial necrosis without reaction".

In cases with arteritic changes the necropsy protocol was analysed and changes, if any, in other arteries were noted. If material for histological examination was available, it was re-examined. The patients' clinical histories were studied.

RESULTS

A. Changes were found in 53 (9.5 %) of the 560 aortic specimens. The age distribution of this group ranged from 39 to 90 years. These preparations were examined further, and arteritis was diagnosed in 8 (1.4 %).

B. Examination of specimens of temporal arteries and two transverse sections of the aorta in 889 cases revealed changes in 102 (11.5 %). Age range 21—95 years. In 16 (1.7 %) cases changes in the aorta or temporal arteries were interpreted as arteritis or sequelae thereof.



Fig. VI:3.

Case VI:1. Ascending aorta. Outer part of media, intima above, adventitia below. In the lower half preserved media with elastic lamellae and elongated nuclei. Media in the upper half necrotic with disappeared nuclei, elastic lamellae slightly thinned and less wavy than normal. No inflammatory cells. "Medial necrosis without reaction". Htx — eos. x 120.

Clinical and morphological data about the patients with arteritis are summarised in Table VI:1. There were seven men and seventeen women, sex distribution male/female 1/2.4. — Three of the patients had had the clinical diagnosis of temporal arteritis which had not, however, been confirmed by biopsy. Five had had vague symptoms, which might be interpreted as polymyalgia arteritica. — Two patients had had a known syphilitic infection and showed arteritic changes in the aorta, but not in the temporal arteries in the one case, where they were examined.

Gross changes in the aorta, other than more or less marked arteriosclerosis, were found in fourteen cases. In cases with arteritis, correlated with polymyalgia arteritica, dilatation of one or more segments of the aorta was seen in seven cases, rupture in two and intimal thickening and wrinkling in three. One case had an aneurysm of the abdominal aorta. In cases of syphilitic arteritis general dilatation was seen in one and rupture in one.

On microscopical examination, besides signs of arteritis, necrotic streaks in the media, "medial necrosis without reaction", were seen in 57 of the 1,459 cases. The nuclei of the smooth muscle cells had disappeared in fairly well circumscribed parts of the media. These areas were mostly found in the middle of the media. The elastic lamellae appeared stretched out and possibly thinner than the surrounding normal ones. There were no inflammatory cells or other reactions in the surroundings (Fig. VI:3). — Necroses were seen in all ages from 36—93 years, but the patients were mostly

over 60 years. There were no signs of manifest or incipient rupture. — The nature of these changes is uncertain, one must think of artifacts. However, literature studies confirm their existence, *vide* General discussion p. 50. — The other changes noted in 98 cases were interpreted as arteriosclerosis with mild inflammation.

CONCLUDING REMARKS

On examination of one section from the ascending aorta arteritis was found in 1.4 % of the cases. On examination of two pieces from aorta plus temporal arteries the frequency of arteritis was 1.7 %. — Three patients had had temporal arteritis, seven more or less obvious polymyalgia and two had had a known syphilitic infection. — Gross changes were seen in about two thirds of the cases, mostly as aortic dilatation.

Table VI:1 Series A

Case nr	Sex	Age	Clin. diagnosis	Poly-myalgia	Main cause of death	Macroscopical changes	Remarks
1	F	70	Infarctus myocardii	—	Infarctus myocardii	—	
2	F	87	Infarctus cerebri	—	Embolia pulmonis Arteriosclerosis uni-versalis	—	
3	M	61	Infarctus myocardii	—	Infarctus myocardii	—	
4	F	99	Peritoneal process	?	Peritonitis, Cystitis necroticans	Dilatation of ascending aorta	
5	F	79	Insuff. valv. aortae	—	Insuff. valv. aortae	General aortic dilatation. Possibly arteritis	Syphilis WR +
6	F	91	Coronary sclerosis Uraemia	—	Pyelonephritis acuta	+	Rheumatoid arthritis 1964
7	M	77	Coronary sclerosis	—	Coronary sclerosis Pneumoniae	Marked arterio- sclerosis	Arteritis in "routine" specimen
8	F	71	Volvulus op.	—	Peritonitis acuta	Narrowing of abdominal aorta	

Cases with arteritis in aorta (series A) and in aorta + temporal arteries (series B) 1971—1972.

+ arteritis or sequelae after arteritis.

— no arteritis.

Table VI:1

Series B

Case nr	Sex	Age	Clin. diagnosis	Poly-myalgia	Main cause of death	Aortitis	Temporal arterit.	Macroscopical changes	Remarks
9	F	74	Carc.colli uteri ?	?	Carc. colli uteri	..	+	—	Syphilis 1919 Case III:13
10	F	74	Mors subita cerebri ? cordis ?	—	Ruptura aortae, aortitis	+	—	Ruptura aortae	
11	F	79	Monocytic leucaemia	—	Monocytic leucaemia	—	+		
12	M	86	Arteriosclerosis univ.	? 1971 ? 1972	Dilatatio aortae	+	+	(right only)	Dilat.asc.+desc.thorac. intimal wrinkling
13	F	64	Morbus Cushing Haemorrhagia cerebri?	+	Infarctus cerebri	+	—	(right only)	1952 E.S.R. 129 mm/lhr
14	F	62	Ruptura aortae?	?	Aortitis, Ruptura aortae	+	+		Case V:4
15	F	72	Stenosis valv. mitralis	1963 ?	Aortitis, Ruptura aortae	+	+		Case III:5
16	M	82	Infarctus myoc. ?	—	Cardiosclerosis Dilatatio aortae	+	+	(right only)	General dilatation of aorta
17	M	72	Ulcus ventr. Infarctus myoc. ?		Ulcus ventr. cum haemorrh	+	+		Intimal wrinkling Aneurysma aortae abdom.
18	F	92	Infarctus myoc. ?	?	Infarctus myoc.	+	+	(left only)	Moderately widened aorta
19	F	93	Infarctus cerebri	+ 1965	Infarctus cerebri	+	+		1965 E.S.R. 100 mm/lhr
20	F	92	Anaemia, Incomp.cordis	—	Arteriosclerosis univ.	+	+		Marked arteriosclerosis
21	F	96	Kystoma ovarii	—	Cystocarcinoma ovarii	+	+		Moderate widening thor. aorta
22	F	89	Insuff. cordis	+ 1957	Endocarditis ulcerosa Insuff. cordis	+	+		Marked dilatation asc. + thor. aorta
23	M	81	Infarctus cerebri	+ 1963	Bronchopneumoniae Arteriosclerosis cerebri	+	+		Dilatation thoracic aorta
24	M	77	Haemorrhagia cerebri	—	Haemorrhagia cerebri	+	+		Intimal wrinkling
								—	1957 E.S.R. 90 mm/lhr

GENERAL DISCUSSION

INTRODUCTION

Among pathological changes in the aorta and the large arteries, those of arteriosclerosis in its various forms occupy such a predominant position that they outshadow those of other diseases, especially since the latter are more or less complicated and masked by arteriosclerotic changes. It may therefore be regarded as significant that the first known independent disease of the arteries, periarteritis nodosa, (Kussmaul and Maier, 1866) affects small and more peripheral arteries, where arteriosclerosis is less prominent. Periarteritis nodosa is a rare disease. — Syphilis was very common far into the twentieth century. Virchow, 1858, in a comprehensive review of syphilitic manifestations only casually mentioned lesions of the vascular system and in some words discussed the relation and morphologic similarities between gummatous and atheromatous lesions. — Malmsten, 1888, in his thesis on aortic aneurysms, quoted a treatise, written by Walshe, 1873, who said that "syphilis may lay the groundwork of aneurysms, as it apparently does of valvular disease also". Doehle, (1885, 1895), produced firmer evidence of arterial involvement in syphilis and, according to Mac Callum (1932), it was a revelation when, at the German congress of clinical pathologists in 1903, Chiari, Benda and Marchand discussed and confirmed the discovery of Doehle and his teacher,

Heller, of syphilitic aortitis. Mac Callum thought the involvement of the heart and vessels to be the most important of all lesions produced by syphilis. One of the reasons why syphilis had not been considered a cause of aortitis earlier was probably that the disease is so often complicated and sometimes masked by arteriosclerosis.

The variation in the conception of the relative importance of different arterial changes is reflected in some handbooks from earlier decades. In Henke-Lubarsch's "Handbuch der speziellen pathologischen Anatomie und Histologie", published in 1924, Jores discussed different types of arteriosclerosis, followed in extent by syphilitic arteritis and a detailed description of periarteritis nodosa. Rare forms, such as purulent arteritis, due to spread from nearby processes, and tuberculous arteritis were also mentioned. In a discussion of aortic aneurysms, syphilitic origin was said to vary from 18,7 per cent, according to Hansemann (1903), to 86 per cent (Heller, 1899, 1903). The basic materials, however, seem to have varied considerably, and the value of these frequency calculations were regarded by Jores as very limited. On the other hand, Jores believed that arteriosclerosis was rarely responsible for aneurysm formation, as it leads mainly to a thickening of the vessel wall. He said: "Im allgemeinen ist die Bedeutung der Arteriosclerose als Ursache der Aneurysmen früher sicher überschätzt worden und eine gewis-

se Vorsicht in der Beurteilung ist am Platz”.

In 1929 Erdheim described an aortic change, which he called medionecrosis aortae idiopathica cystica. This disease has since been regarded as the most common cause of dissecting aneurysm.

At roughly the same time aortic changes in rheumatic fever and rheumatoid arthritis received considerable space in the literature. Klinge (1933) stressed that such rheumatic arterial changes predisposed to aortic atherosclerosis more often than widely supposed.

In Kaufmann's "Lehrbuch der speziellen pathologischen Anatomie" (1955) Staemmler gave roughly equal space to the discussion of syphilitic arteritis and periarteritis nodosa. Thromboangiitis obliterans (Winiwarter-Buerger) was treated in some pages and arterial changes in rheumatoid arthritis and rheumatic fever were discussed rather extensively. Giant cell arteritis, however, which had been described by Horton et al. (1932), was treated rather briefly. Interest in this form of arteritis and the discussion of the relation between temporal arteritis and more widespread arterial processes have since increased considerably. Some descriptions published as early as in the 1890s probably concerned the same disease (Hutchinson 1890). A detailed discussion of the earlier literature and of the opinions expressed is given in Hamrin's (1972) thesis. Similar and possibly identical arterial changes have been described under a wide variety of names. The clinical picture is variable and different aspects have been stressed by different authors. A recent review of a clinical material with pathological correlations and an extensive list of references was published by Hamilton *et al.* (1971)

It may now be regarded as highly probable that generalised arterial disease (giant cell arteritis, temporal arteritis) is responsible for the wide variation of clinical manifestations though the aetiology and pathogenesis of the

arteritis are unknown. The name polymyalgia arteritica, suggested by Hamrin et al. (1964), seems to be the most appropriate. As the changes in the large arteries appear to be morphologically characteristic it may be regarded as an independent disease. Hudson, in his book on Cardiovascular Pathology, published in 1965, gave an ample review of temporal arteritis, which emphasised the widespread arterial changes and differentiation of the disease from syphilitic aortitis, polyarteritis nodosa, Buerger's disease, tuberculous arteritis, and Takayasu's disease. Takayasu's disease or aortic arch syndrome is most common in quite another age-group, but it is clear also from Hudson's work that many investigators tend to regard it as a similar type of arteritis. In a large supplement (1970), Hudson discussed the clinical picture of polymyalgia rheumatica and its relation to arteritic changes, and the name polymyalgia arteritica was taken up for discussion. The condition is thus now accepted as a separate disease and discussed as such in reviews. The number of cases described by individual contributors is, however, small, and it is not possible to obtain an idea of the frequency of the disease. It was with this in mind that the present investigations were undertaken, and the results will be discussed.

PATHO-ANATOMICAL PICTURE OF ARTERITIS IN POLYMYALGIA ARTERITICA

The material described in paper I included 8 of the cases that were studied in detail and followed up by Hamrin. The clinical picture was thus well known and could be correlated with the patho-anatomic changes. The other cases in this investigation contributed to elucidate the development of the disease. Studies, described in Chapter III, supplemented by

investigations of further cases. The patients were not followed by any physician particularly interested in the disease, but their history was known, and, in 3 cases, temporal arteritis had been verified by biopsy. In a fourth, the clinical picture had motivated treatment with corticosteroids. Three cases were included because of gross aortic changes at necropsy. Three patients had "rheumatic" diseases of different kinds and the investigation included 5 cases with previously known syphilis in an attempt to find clues for distinguishing arteritis in polymyalgia arteritica from syphilitic arteritis. One case with dissecting aortic aneurysm and medionecrosis, associated with Marfan's syndrome, was studied.

MACROSCOPICAL CHANGES

The macroscopic picture of arteritis in polymyalgia arteritica is generally not diagnostic. Dilatation of the aorta is common. Intimal changes with wrinkling may be seen and sometimes a distinct thickening with mother-of-pearl like appearance. The large branches of the aortic arch may show both widening and narrowing with mural thrombi. Intimal changes are most common in the ascending aorta and aortic arch. In one case (III:9) intimal thickening was prominent in a limited part of the abdominal aorta. Similar intimal changes have been described in other, possibly related, arteritic conditions in young Africans (Isaacson 1961) and as local changes in the aortic wall in cases of so-called non-syphilitic aortitis described as a part of an arteriosclerosis investigation from Central America (Restrepo et al., 1969). The American patients were mostly below 44 years, most of them 35—44 years old. The changes were somewhat more common in men than in women. Local arteritis of the abdominal aorta in 4 patients, 17—24 years of age, 2 women and 2 men was described by Lewicki and Rykowski (1969). These cases were diagnosed clinically,

and the patients improved after partial resection of the aorta and insertion of a graft.

MICROSCOPICAL CHANGES

The microscopic changes in temporal arteritis are characteristic with oedema of the wall and areas of fibrinoid necrosis, in earlier stages abundant round cells as well as polymorphonuclear leukocytes. Also multinucleated giant cells occur, mainly around the disintegrating membrana elastica interna (Fig. III:1). Somewhat later the vessel shrinks with narrowing of its lumen, fibrosis of the intima and adventitia, accumulations of small numbers of lymphocytes and single giant cells (Fig. III:2). — Judging from the findings in paper II, arteritis causes irreversible, recognisable changes with contraction, narrowing of the lumen and fibrosis, especially in the adventitia.

The development of the changes in the large arteries cannot be followed in the same way, as biopsy cannot be done. The disease is chronic and rarely fatal and then usually late in the course. Therefore, the early stages are less well known. Relatively acute changes were described by Frangenheim (1951) in a patient with a history of possibly 5 months, by Lander and Bonnin (1956) in a case with a history of one (?) month and by Sproul and Hawthorne (1937) in a patient without known previous disease. In these cases widespread destructions of the media and adventitia with infiltration of lymphocytes, plasma cells and giant cells were described. These articles were discussed in paper I, page 154. — Three patients, described in Chapter III had a short history; a woman who was 85 years old had been ill for only 2 months. In this case and some of the others the outer media of the large arteries was oedematous with moderate round cell infiltration (Fig. III: 6, 13, 14). Some smaller arteries showed cushion-like intimal thickenings, made up of relatively cellular tissue (Fig. III:5). These thickenings were most-

ly not seen at exactly the same sites as the medial changes, but appeared to belong to the picture of arteritis. — In two cases with a history of 8 and 9 months, respectively, (1,7) there were similar oedema and destruction of the outer media with abundant deposition of round cells, in the latter case also some multinucleated giant cells (Fig. III:3, 4). Of patients with a longer history, most had circumscribed medial changes of necrotic appearance with loss of nuclei and collapse of the elastic lamellae (Paper I. Figs. 9, 11, 12, 13, 16; Fig. III:7, 8, 9, 15). Particularly around breaks in necrotic parts of the media there was round cell infiltration and, in many cases, multinucleated giant cells. Giant cells were not a constant finding and could represent a non-specific reaction to necrotic material, as suggested by Hamperl (1953) and Isaacson (1961). The name giant cell arteritis therefore seems but little appropriate, but is probably too well established to be changed.

Localisation in the arterial wall

Oedema and circumscribed necroses were found in the medial layer, most often its outer parts, with a narrow or wider zone of preserved elastic lamellae nearest the intima. Sometimes the intima showed atheromatous plaques with fibrosis and fat vacuoles, though fairly mild and apparently not affected by, or interfering with, the medial changes. The intimal thickening observed in several cases and possibly most pronounced in young women, No XII in Paper I (Paper I Figs. 14, 15) and No 9 in Chapter III (Fig. III:11), appeared, as mentioned, not to have anything to do with the medial changes. They might be manifestations of a non-specific reaction, though of unusual appearance, but probably belonged to the picture of arteritis. Deposits of fibrin could be found on the surface, and the cellular thickenings might be regarded as a stage of organisation of fibrin thrombi. Similar in-

timal cushions were also seen in case III:1 (Fig. III:4, 5) and therefore do not appear to be related to the patient's age alone. — The adventitial changes were mild, in some cases there was moderate fibrosis. No changes in the vasa vasorum could be seen.

Course of the microscopical changes

It thus appears to be possible to follow the development of the arteritis from a more diffuse oedematous change of the media to collapse and necrosis and subsequent disintegration of the structure as, for example, in case V in Paper I (Paper I, Fig. 9), where, in some specimens, only minimal fragments of disintegrating elastic lamellae were found in a fibrous scar tissue and where the descending aorta was aneurysmally widened and ruptured. Although the changes appeared to occur in a certain sequence, different stages could be recognised in one and the same case in sections from varying parts of the arterial system.

LOCALISATION IN THE ARTERIAL SYSTEM

The localisation and extent of the arterial changes is seen in Fig. II:1 and III:19. They were most common in the aorta, and there in the ascending part, but could also be seen in parts of the descending thoracic aorta or abdominal aorta. Involvement of the cephalic branches was more common than that of the caudal branches. In some cases the arteritis was complicated by thrombosis (Paper I, cases I, V, VI, XIII, Case III:2). Branches other than those shown in the diagrams were also affected; in the investigation described in Chapter III arteritic changes or sequelae were found in five of six temporal arteries studied, in three of six coronaries, and in one of four cases, where the basal cerebral arteries were examined. The pulmonary artery was studied in three cases, but no arteritic changes were

found. No certain arteritic changes were seen in the renal arteries, which were examined in eleven cases. — These findings confirmed that even smaller branches may be involved and that temporal arteritis is only a part of a more widespread vascular disease.

The changes described here refer to cases with a clinical picture of polymyalgia arteritica, temporal arteritis or Takayasu's disease. According to the discussion in Paper I, the arterial changes in Takayasu's disease are largely the same as those seen in polymyalgia arteritica. This impression is also gained from the somewhat brief reports of the changes in Takayasu's disease, emanating, from, above Japan. They have been described by Nasu (1963), Ueda et al. (1968) and Oota (1972).

COURSE OF POLYMYALGIA ARTERITICA

This work is not devoted to the clinical picture. It may, however, be stressed that polymyalgia arteritica runs a chronic course. The three patients in Chapter III, who died some months after they had symptoms of polymyalgia died from apparently unrelated causes. Most patients who die of true complications seem to do so in a chronic stage from dilatation or rupture of the aorta. However, Du Pont & Heerup (1948) described a most interesting case from Denmark, where the patient died after some months of continuous deterioration, apparently caused by widespread arteritis.

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS “RHEUMATIC” DISEASES

A few cases of rheumatic disease were included in the material — the picture in a woman with juvenile rheumatoid arthritis (III:9) did not differ in respect of vascular changes from

the other cases. The information about the rheumatic disease in case III:8 is diffuse and suggests, if anything, relatively acute rheumatic fever in the 1940s with persistent valvular changes of the heart. The picture of the arteries resembled that in cases of polymyalgia arteritica. In the literature the rheumatic arterial changes are described as resembling those in syphilis with adventitial fibrosis and defects in the media with connective tissue scars, localised around penetrating capillaries. Adventitial fibrosis was seen in case III:8 (Fig. III:10) and in case III:9 (Fig. III:12), which both had some “rheumatic” affection. No marked thickening of the vasa vasorum like that of syphilitic arteritis was observed. The “rheumatic” affection of the arteries in all three cases had probably occurred a long time ago and the changes appeared as residues. The acute stages might reveal more of the nature of the arteritis. — My material is too small to warrant conclusions about the patho-anatomic picture of arteritis in rheumatic fever and rheumatoid arthritis. It might be difficult to decide whether symptoms of polymyalgia may have been concealed in patients with persisting rheumatoid arthritis. — Summing up, it would appear that aortic changes in rheumatic fever and rheumatoid arthritis are not sufficiently well known and identified because most of the publications date back to a time when polymyalgia arteritica was an unknown disease. — Aortitis has been found in cases of spondylarthritis. This problem and the occurrence in the Malmö material is receiving attention by Berge et al.

Syphilitic aortitis

Figures given for the frequency of arteritis in syphilis vary. Formerly, when syphilis was very common, aortitis was also common. In his book on aortic aneurysms, Malmsten (1888) regarded syphilis as responsible for 86 % of all aneurysms. In the latest investigation from

Norway by Gjestland (1955) the frequency of cardiovascular manifestations was given as about 10 % in a clinically followed material of about 1,000 cases of untreated syphilis. Seventy-five per cent died from these cardiovascular lesions. In a study from Newcastle by Mac Farlane et al. (1956) 62 % of patients with cardiovascular involvement had aortic valve incompetence and 21 % aortitis with dilatation, 16 % aneurysms. — During the time the present material was being collected, 5 cases of syphilis came to necropsy. The large arteries were examined systematically in the same way as in the cases of arteritis.

The macroscopic picture of syphilitic aortitis is described as very characteristic with changes above all immediately distally to the valves with upward spread in the aortic arch. The aorta may be widened within this area or within a segment more distally thereto. The intima is thickened and wrinkled with irregular, contracted scars. The thickening may cause narrowing of the origins of the coronaries and possibly of the large branches from the aortic arch. There is often atheroma with calcifications, which make the specific changes less easy to detect. The changes are generally seen in the chronic cicatricious stage as the disease is most often not fatal, and the patients may have survived their primary affection for several decades. — The microscopic changes are described as a thickening of the walls in the vasa vasorum with narrowing of the lumen and dense lymphocyte infiltrates in the surroundings. Impaired blood supply to the outer parts of the aortic wall is believed to lead to hypoxia with destruction of the media around the vessel branches. Fibrous tissue proliferates from the adventitia with irregular scarring as a result. The weakening of the vessel wall by scar formation might explain complications like aneurysms and ruptures. The patients in the present material lived for many years after the primary affection. One of them, III:13

died of a complication of aortitis with aortic rupture 53 years after treatment of her syphilitic infection. This aortitis resembled the type seen in polymyalgia arteritica and might be supposed not to be of syphilitic origin, though the changes were largely masked by arteriosclerosis. Two patients died from valvular complications, which were related to the syphilis, and the other two died from unrelated diseases. — Barely any definite gross changes were seen, and the microscopic alterations were limited to moderate adventitial fibrosis, though, in two of the cases, there was a distinct thickening and narrowing of the vasa vasorum (Fig. III:16). The picture differed from that of polymyalgia arteritica and suggested that these two forms of arteritis do not have the same pathogenesis.

MEDIONECROSIS AORTAE IDIOPATHICA ERDHEIM

In this disease a loosening of the media which may result in the formation of true cysts is found. There is an increased occurrence of metachromatic material and no inflammatory reaction. The same anatomic changes are seen in Marfan's syndrome, of which I studied one case (Fig. III:18). Rupture of the aortic wall and dissecting aneurysm commonly lead to the discovery of these cases. The rupture generally causes immediate death, and it is not possible to draw any conclusions on the age of the changes or their course of development. In ruptures with dissecting aneurysms a diagnosis of medionecrosis aortae may be taken for granted. In the retrospective survey of arterial changes, however, one case of arteritis with dissecting aneurysm was found. (Case V:I). — Degeneration of the media in Erdheim's disease was described by him (1929) as idiopathic. He discussed various aetiological possibilities and described a "typical" case of aortic rupture with dissecting aneurysm in

which necropsy findings were ascribed to syphilitic aortitis. He did not, however, find any inflammatory changes or "any histological similarity at all with mesaortitis luica". Erdheim thought that the loosening of the ground substance might be due to insufficiency of the vasa vasorum of some other nature with secondary necrosis of the media. The lack of an inflammatory reaction should argue against inflammation as a cause of destruction of the components of the wall. A humoral destruction, possibly some toxic effect, might be the explanation. — In recent years (Grant and Prockop 1972) this opinion of medionecrosis has been extended by the finding of a change in the tropocollagen with dissolution of cross-linkings. Patients with Marfan's syndrome have these collagen changes in different organs and it might explain the loose skin, the flabbiness of the lens capsule and the skeletal deformities, which occur together with the looseness and brittleness of the aortic wall. A similar change of the collagen occurs in homocystinuria and in lathyrism. In the latter condition dissecting aneurysm may also occur and has been described in man, as well as in animals. Here then, we have come closer to the pathogenesis of the disease although, we do not know the background of the spontaneous changes in the ground substance. A difference in development and tissue reaction between medionecrosis and arteritis in polymyalgia arteritica argues against the two diseases being of the same nature.

MEDIAL NECROSES WITHOUT REACTION

Gsell (1928) described mural necroses of the aorta as an independent disease and discussed their relation to spontaneous aortic rupture. He reported seven cases, all with acute collapse and death from aortic rupture. In sections from the aorta he found necrosis in the

media, *i.e.*, cell-free areas with death of muscle cells and changed elastic lamellae, which were thinner and more closely packed than normally, with changed stainability. In some cases with healed earlier ruptures, the continuity of these changed lamellae was interrupted by ingrowing connective tissue. Otherwise no inflammatory reaction was seen. The cause of these medial necroses was discussed, but considered obscure. Gsell stressed that similar changes can be experimentally produced by injection of adrenaline and discussed a toxic effect on the aorta. He emphasised that three of the patients had hypertension with renal insufficiency and uraemia, and in one case the patient was a heavy smoker and had chronic sepsis. It appears that Erdheim thought that the changes, described by Gsell, were partly the same as the medionecrosis. Gsell, however, did not mention any loosening of the media and his cases seem, according to the descriptions and illustrations to be of different types. — In the present investigation the "medial necroses without reaction" resembled those described by Gsell. At examination of pieces of the aorta from a one-year necropsy series they were seen in 57 (4%) of 1,459 cases. They were found in subjects, aged 36—93 years, but mostly after 60 years of age. None of these cases had aortic rupture. This type of necrosis is probably difficult to discover when associated with rupture and dissection; neither was it observed in the retrospective investigation in cases with rupture or dissection.

The findings in the present investigation are just as non-informative as Gsell's regarding the cause of these necroses. — One of Gsell's illustrations showed defects in the necrotic media with ingrowing connective tissue, a picture resembling that in the present cases, especially in so-called Takayasu's arteritis in a 17-year old girl and juvenile rheumatoid arthritis in a 22-year old woman. Gsell's case was seen in a 26-year old woman and might very well

have been an instance of chronic arteritis. In Gsell's case histories nothing is said of polymyalgia symptoms.

Manley (1964) examined 27 cases of dissecting aneurysm of the aorta, where microscopic specimens were compared with corresponding sections from age- and sex-matched hypertensive and normotensive patients. In all cases he found a varying degree of metachromasia, which was, however, somewhat more pronounced in those with dissection (30 % of these had a high degree of metachromasia). A certain loosening of the medial structure was common, and true cyst-like spaces were seen, mainly in the cases with dissecting aneurysm. Some fragmentation of elastic lamellae was observed in all three series, though most often in association with dissection. Muscle cell necroses of the same type as those described by Gsell were not infrequently noted — more often in cases with dissection or with hypertension. In two cases with dissecting aneurysm infiltration of inflammatory cells was found, and the picture agreed with that of so-called giant cell arteritis. One case of dissecting aneurysm of the aorta due to "giant cell arteritis" was described by Harris (1963). Summarizing, medionecrosis aortae mixes up with other, obscure, medial necroses and some of the earlier described cases may have been polymyalgia arteritica (or Takayasu's disease).

POLYARTERITIS NODOSA

Arteries up to some millimeters in diameter are engaged in this disease. It runs a more fulminant course than polymyalgia arteritica, and more often leads to complications with infarctions in vital organs, *e. g.* kidneys, myocardium etc. In some respects the microscopic picture may resemble that of arteritis in polymyalgia arteritica, but in my cases of polyarteritis nodosa no changes were seen in the large arteries. One patient (V:5) in the retro-

spective investigation had changes in the temporal arteries, which did not differ from those often seen in temporal arteritis. Similar lesions were, however, found in the vessels of the same caliber in the kidneys and other organs, and the disease must be regarded as polyarteritis nodosa. — The generalised arteritis of large arteries and polyarteritis nodosa appear to be different, but changes of both types may be seen in one and the same medium-sized or thin artery.

FREQUENCY ANALYSIS

Temporal arteritis, so-called giant cell arteritis and polymyalgia arteritica have been regarded as rare diseases. Earlier reports, have, however, been based on a mixture of clinically observed and pathologically studied cases, and not correlated to a defined population. The investigations in Malmö provide a basis for certain statistical calculations.

CLINICAL INCIDENCE OF POLYMYALGIA ARTERITICA

Within 7½ years Hamrin found 94 cases in a population of somewhat more than 100,000 inhabitants. This would mean an incidence of 12 cases per 100,000 inhabitants per year. He stressed, however, that the number of cases diagnosed varied with the interest in the disease and the energy with which such cases were sought. At the Institute of Pathology in Malmö, the only one in the town, which has about 260,000 inhabitants, on the average 11 biopsy specimens are examined per year for temporal arteritis, 5 with changes of arteritis and 6 without. Assuming that biopsy is done in all clinically suspected cases of temporal arteritis, the clinical incidence would be 4 cases per 100,000 inhabitants per year. Arte-

ritis confirmed by histological examination of biopsy specimens would occur in about 2 cases per 100,000 persons per year. The wide variation of these incidence figures must reflect differences in interest in the disease. More reliable information could be obtained by an investigation of the pathological changes at necropsy.

FREQUENCY OF ARTERITIS IN NECROPSY SERIES

Malmö is well suited for frequency studies because the Institute of Pathology serves all hospitals in the town and all together 98 % of all patients dying in hospital are necropsied (65 % of all deaths in the population of the town). Frequency studies were performed as a retrospective investigation of necropsy material from 15 years (1957—1971). — Besides the former analysis of temporal arteritis in a one-year material (Paper II), one piece from the aorta was collected at all necropsies during 6 months, and two pieces from the aorta plus temporal arteries during the following six months for screening for arteritis (prospective studies).

In 79 cases of 20,591 necropsies in the retrospective material active arteritis or sequelae after arteritis were found. The frequency was 0.4 %. The age distribution, as given in Fig. V:6, revealed that some cases occurred in younger persons but most in elderly (70—89 years old). — In the prospective investigation of temporal arteritis (Paper II) arteritis or sequelae were seen in 1 %. At examination of one section from the aorta, changes were found in 1.4 %, and in the material with two pieces from the aorta plus temporal arteries in 1.7 %. These prospective studies thus gave up to four times a higher frequency than the retrospective analysis, and all these necropsy studies a much higher frequency than that of clinically diagnosed polymyalgia arteritica or temporal arte-

ritis. Analysis of a clinical material gives incidence figures, which cannot be directly compared with prevalence figures from necropsy studies. If the frequency of arteritis found at necropsy is assumed to be a summation of 10—20 years' incidence figures, the frequency in the necropsy series is still very much higher than the number of clinically observed cases. — The findings suggested that arteritic changes would be discovered even more often if more material had been examined and that changes in the aorta are probably more common than in the temporal arteries. Since the arterial lesions are patchy and not continuous, there is a considerable chance that few and small specimens will miss the arteritic changes.

CORRELATION OF ARTERITIS FOUND AT NECROPSY WITH CLINICAL SYMPTOMS

In the retrospective series, 38 of the 79 patients, barely 50 % (Table V:5) had had histologically verified temporal arteritis, or a clinical history suggesting polymyalgia arteritica. In the other cases there were no notes about polymyalgia. Many of the patients, however, were in a very poor condition when last admitted to hospital and succumbed to cerebral or acute cardiac diseases and no informations about earlier symptoms were available. The material was entirely unselected and an examiner especially interested in the disease would surely be able to obtain much more information. It is clear from Hamrin's investigation that also the way in which the patient's history is taken is of significance, because the symptoms are often so diffuse that the patients are not aware of what they should complain about — Close analysis of the E.S.R. was not possible in this material. — Twenty-nine of 79 patients (38 %) died from complications of arteritis, mostly aortic rupture. Twenty-one patients (28 %) had 30 aneurysms of the

aorta including 10 with rupture. — Twenty patients (25 %) had a general widening of the aorta and 13 (16 %) aortic rupture, but not on the basis of aneurysm.

In the prospective series with all together 36 cases of aortitis or temporal arteritis four patients had had clinical temporal arteritis and fifteen questionable symptoms between two months and twenty years before death, respectively, which could be interpreted as polymyalgia arteritica. Forty-seven per cent had no notes about previous polymyalgia. — The remarks about the clinical interest are applicable to these series, as well as to the retrospective studies.

In the retrospective study the number of cases of arteritis, diagnosed in different years, tended to rise, especially after 1968. This reflects the importance of an increasing interest, both in vague clinical symptoms and in gross changes at necropsy. These figures of the frequency or arteritis changes found must therefore be regarded as minimum figures. The picture of arteritis is complicated by arteriosclerosis, and typical changes may be difficult or impossible to discover. Erdheim, in his description of medial changes in syphilitic arteritis and medionecrosis, stressed this and made a comparison with stars, which are only partly seen when there are clouds in the sky.

Increased clinical interest would probably also reveal a much larger number of cases. The patients naturally have more or less obvious symptoms. Even though we do not know the etiology of polymyalgia arteritica, we can today offer prompt relief by corticosteroids. Such treatment is probably not curative but it may perhaps prevent, or at least retard, further development of the arteritic changes. Pictures of healing, were apparent in some of the systematically examined cases, where e.g. III:4 had only mild arteritic changes after having been treated with corticosteroids for 10 years. — The disease is chronic. In most cases it

runs a benign course and heals with sequelae. According to the retrospective investigation, complications are common, particularly ruptures. Whether it is possible to prevent such complications by corticosteroid therapy is not known.

OTHER FINDINGS IN RETROSPECTIVE MATERIAL (AORTIC ANEURYSMS)

As by-products of the investigation of the frequency of arteritis in a 15-year material, it might be mentioned that 66 (0.4 %) of 20,591 persons necropsied had more or less well documented syphilis. In 44 of these 66 cases (66 %) fairly typical arterial changes were found. The frequency of complications with death from arterial rupture was lower than in arteritis, 13 (20 %) of 66 cases, aneurysms were seen less often and their distribution differed from that of aneurysms in arteriosclerosis and arteritis. Strikingly many syphilitic aneurysms were found in the ascending aorta and arch.

The overwhelming majority of aortic aneurysms were caused by arteriosclerosis. The aetiology of aortic aneurysms has been discussed for more than 100 years. Malmsten (1888) found that 86 % of the aneurysms were due to syphilis, the present investigation suggests that to-day the main cause of aneurysms is arteriosclerosis (85 % of all aneurysms). This was shown by Carlsson and Sternby (1964) in an investigation of part of the same material (1957—1961) from Malmö, consisting of 5,386 cases. One hundred and thirteen aneurysms in 97 patients were described (1.8 % of necropsy material). Seventy-five per cent of the thoracic and 97 % of the abdominal aneurysms were due to arteriosclerosis. The present investigation revealed aneurysms in 2 % of the cases. Fifty-nine per cent of the thoracic and 92 %

of the abdominal aneurysms were of arteriosclerotic origin, while arteritis was responsible for 15 % of the thoracic and 5 % of the abdominal aneurysms, and syphilis for 26 % of the thoracic and 3 % of the abdominal aneurysms. Complications in the form of rupture were most common in patients with arteriosclerotic or arteritic aneurysms.

CONCLUDING REMARKS

Arteritis in polymyalgia arteritica is thus a disseminated arterial disease with a relatively characteristic picture, differing from arteritis in syphilis. It is not possible to distinguish arterial changes in Takayasu's disease because; in many respects the histological picture re-

sembles that seen in polymyalgia arteritica. The occurrence in different age groups might explain the fact that they were formerly regarded as different entities. A few cases of typical giant cell arteritis have, however, been described also in young persons, for example, changes in the basilar artery in a girl, about 10 years old, who died from brain infarction after prodromal symptoms for a few days (Marsden 1972).

The increase in the number of cases described in recent years might suggest that it is a new disease. It appears, however, that once an examiner is aware of the disease, he will be able to find an increasing number of cases, both from a suggestive clinical history and on gross and microscopic examination of the large arteries.

CHAPTER VIII

SUMMARY

Chapter I. As arteriosclerotic processes are so common in the aorta and the large arteries, cases of aortitis and arteritis may pass unrecognised. It was not until the beginning of the twentieth century that syphilitic arteritis was defined as a specific entity. — General arteritis in connection with temporal arteritis and polymyalgia rheumatica have been described since the 1930s. Among others, Hamrin *et al.* (1964) found evidence of widespread arteritis in these cases and coined the term "polymyalgia arteritica". Though the changes are known and described in the literature, little is known about their development and spread in the arterial system or their frequency.

Chapter II (Paper I). The morphological changes in the large arteries were studied in six patients with clinically investigated polymyalgia arteritica, which had been followed up for many years, two with the clinical picture of morbus Takayasu, four with temporal arteritis, clinically known or verified by biopsy and two with gross aortic changes, presumably of arteritis. The large arteries were studied microscopically in about 100 transverse sections per case and the extent of arteritic changes was registered (Fig. II:1). The microscopical changes were described in detail. — The essential lesions were located in the outer part of the medial layer; in early stages oedema with lymphocytic infiltration was seen, later on, patchy necroses. Around breaks in necrotic media there were accumulations of

lymphocytes and plasma cells, sometimes multinucleated giant cells. In some cases the media had been replaced by connective tissue scars. — The arteries were examined in the same way in two patients with polyarteritis nodosa, but no changes were found in aorta or its main branches.

Chapter III. The same types of investigations were performed on a further sixteen cases (five with temporal arteritis, five with gross aortic changes, suggestive of arteritis, five with syphilitic arteritis and one case of Marfan's syndrome with dissecting aortic aneurysm). The characteristics and the course of the arteritic changes were described on the basis of the clinical history of the patients. The findings agreed with and strengthened those in the former study (Paper I). The extent of the lesions was registered (Fig. III:19) and confirmed the disseminated occurrence, seen in the earlier cases (Fig. II:1). — The characteristics of arteritis in polymyalgia arteritica were related to those of syphilitic arteritis. The latter showed adventitial fibrosis and thickening of the vasa vasorum, which was not found in arteritis in polymyalgia arteritica.

Chapter IV (Paper II). Temporal arteries from 1,097 necropsies in Malmö were studied microscopically. Temporal arteritis or sequelae after arteritis was found in twelve cases (one per cent). Two of the patients had had temporal arteritis, seven had formerly had symp-

toms, which might have been manifestations of polymyalgia arteritica, though they were not diagnosed as such. — The microscopical picture of temporal arteritis in different stages as well as of residues was described. The frequency of arteritis of 1 % was correlated with the clinical incidence, according to temporal artery biopsies in the same population, four cases per 100,000 inhabitants per year. — Signs of arteritis were thus found far more often at necropsy than the formerly supposed frequency of arteritis would indicate.

Chapter V. Retrospective study of arterial changes in 20,591 necropsy cases from Malmö during the years 1957 — 1971. Cases with a diagnosis of giant cell arteritis, temporal arteritis, unspecific arterial inflammation, polyarteritis nodosa, syphilis, "rheumatic" arterial disease, medionecrosis aortae and dissecting aneurysm, rupture and aneurysm of aorta were studied. All together 658 cases with arterial changes were examined, in 307 of these material for microscopical investigation was available.

79 cases of arteritis were found (0.4 %), 38 of these had had temporal arteritis or clinical signs of polymyalgia arteritica. Twenty-nine (37 %) of the 79 patients died from aortic rupture or other complications of arteritis. The material was unselected and the cases were primarily observed by different members of the staff. The frequency figures are surely too low. It might be mentioned that during later years, when interest in polymyalgia arteritica had been aroused, the frequency of such cases markedly increased.

The frequency of aortic aneurysms was registered as well as their site, size and complications. 377 (85 %) of 443 aneurysms were classified as arteriosclerotic, 36 (8 %) as syphilitic and 30 (7 %) as caused by arteritis. This gave quite another view of the causes of aneurysms than that in the former part

of this century. — Aortic rupture (aneurysmal or non-aneurysmal) was found in 37 % of cases with arteritis, 14 % of arteriosclerotic aneurysms and 8 % of syphilitic aortitis. — Aortic rupture with dissecting aneurysm was found in 41 cases. One of these was caused by arteritis, the others were classified as medionecrosis aortae idiopathica (Erdheim).

Chapter VI. Prospective study of necropsy cases during one year in Malmö. In series A (first half-year) one transverse section from the ascending aorta was studied (560 cases), in series B (second half-year) temporal arteries and two transverse sections from the aorta (ascending part and at the level of the diaphragm) were studied (889 cases). — The frequency of arteritis found in series A was 1.4 % and in series B 1.7 %. Examination of the aorta and still more of double sections from the aorta plus temporal arteries thus gives a higher frequency than examination of the temporal arteries alone (Paper II). This seems reasonable as the arterial lesions are disseminated and often patchy and do not seem to spread continuously. Three of twenty-four patients with arteritis in the aorta or temporal arteries had had temporal arteritis, five had had symptoms, which could be interpreted as polymyalgia arteritica and two had been known to have a syphilitic infection. — This analysis thus further stressed that polymyalgia arteritica is far more common than the cases diagnosed clinically.

Chapter VII. A short historical review of opinions about arterial changes. The macro- and microscopical pictures of arteritis in polymyalgia arteritica are discussed with differential-diagnostic considerations against other types of arteritis.

The relation between polymyalgia arteritica and Takayasu's disease is discussed. There are anatomical similarities, but their occurrence

in different age groups (and perhaps their geographical variation) is puzzling. As Takayasu's disease seems so very rare in Scandinavia it is difficult to form an opinion of the nature of the changes.

Arteritis in rheumatic fever and rheumatoid arthritis has been described. The later stages of these changes seem rather uncharacteristic. The small number of cases of "rheumatic" disease examined does not permit any conclusions. Symptoms of polymyalgia might well be masked by persisting rheumatic disease.

Syphilitic arteritis has different characteristics microscopically, but an earlier confusion of the diseases cannot be excluded.

The differentiation from medionecrosis aortae idiopathica is not difficult as this lesion does not show any inflammatory reactions. Typical arteritis was found in one case of dissecting aneurysm, which is usually automatically ascribed to medionecrosis aortae. The different morphology gives reason to believe that arteritis in polymyalgia arteritica differs in pathogenesis from medionecrosis aortae.

The frequency of arteritis of the type seen in polymyalgia arteritica is discussed from its occurrence in clinical materials and the fre-

quency of morphological changes found at necropsy, which is much higher. The investigations give no clue to the aetiology of arteritis in polymyalgia arteritica, which was also primarily beyond the scope of the studies.

In conclusion it would appear that:

- 1) polymyalgia arteritica seems to have as an anatomical substrate a widely disseminated arteritis in the aorta and other large arteries;
- 2) the lesions have a rather characteristic gross and, above all, microscopic picture and the disease appears to be an independent entity;
- 3) arteritis or sequelae after arteritis in prospective studies of necropsy materials is found in up to nearly two per cent, and this must be a minimum figure;
- 4) the disease seems very often to pass undiagnosed clinically, and an increased interest in the disease leads to a much more frequent discovery of the condition;
- 5) the course of the arteritis is mostly benign, but complications, mainly aortic rupture, occur in quite a number of cases; and
- 6) the arteritis is not a "new" disease, but may earlier have been overlooked or not differentiated from other arterial changes.

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